

# Part I - Synthetic Studies on the Teleocidin Alkaloids. Part II - Catalytic Asymmetric Reactions of Enecarbamates with Dicarbonyl Compounds. Part III - A Transannular Mannich Approach to the Polycyclic Alkaloids: Synthetic Studies on the Cylindricine Alkaloids

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# Part I - Synthetic Studies on the Teleocidin Alkaloids

# Part II - Catalytic Asymmetric Reactions of Enecarbamates with *α,α'*-Dicarbonyl Compounds

# Part III - A Transannular Mannich Approach to Polycyclic Alkaloids: Synthetic Studies on the Cylindricine Alkaloids


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Para os meus pais, que abandonaram muitos dos seus sonhos para que eu pudesse perseguir os meus.

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# PREFACE

The present thesis is submitted in candidacy for obtaining the Ph.D. degree from the Department of Chemistry, The Technical University of Denmark (DTU). The Ph.D. stipendium was kindly provided by the Portuguese Foundation for Science and Technology (FCT).

The thesis is composed of three independent parts, the various chapters being independent with respect to the references presented therein. Part I and III deal with the total synthesis of the teleocidin and the cylindricine alkaloids, respectively, and the corresponding work was performed at the DTU over a period of approximately 4½ years, under the supervision of Professor David Tanner. I would like to express my gratitude to Professor Tanner for the stimulating research projects provided and for allowing me to work as independently as I wished. Part II corresponds to the work performed during a 7 months stay at the Graduate School of Pharmaceutical Sciences, The University of Tokyo. This part of the thesis deals with the development of catalytic asymmetric addition reactions of enecarbamates to carbonyl compounds and it was carried out with the supervision of Professor Shū Kobayashi. I would like to thank Professor Shū Kobayashi for the opportunity to work in his research group. All the Kobayashi group members are acknowledged for making my stay in Japan a truly memorable life experience. In particular, I would like to thank Ryosuke Matsubara, with whom it was a pleasure to work and socialize. It should be mentioned that some of the results presented in Part II were obtained in collaboration with Matsubara-san. In particular, most of the experiments in Table 4.10, Chapter 4 (Part II) should be credited to him. Fabrice Robvieux, the other western in the Kobayashi group, also deserves a special mention for introducing me to the pleasures of Karaoke (!), exotic food and for the regular Saturday walk to the nearby sento.

A very special note of appreciation goes to my laboratory partners during my various stays at the DTU, Thomas E. Nielsen, Jakob Feldthusen and Anne-Lene Hansen. They are to be credited, among countless other things, for stoically putting up with my latin temperament. The other members of the Tanner group with whom I overlapped are acknowledged for creating a great working atmosphere, where all sorts of topics could be discussed with a good dose of humor. In particular, Martin Juhl (the talented “Mr. Name Reactions”), “dating expert” Mikkel Jensing, “hard-disk” Jens Nolsøe, “dark-humor” Thomas Hjelmgaard and “multitask” Janne Tønder (who, among other things, is a sight for sorrow eyes!) are acknowledged for many good moments.

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Invaluable comments and corrections on parts of this thesis by Jens Nolsøe, Jakob Feldthusen and Morten Jørgensen are gratefully acknowledged. Furthermore, the “Danish Abstract” was kindly provided by Morten Jørgensen.

Paulo Jorge Vieira Vital
Copenhagen
November 2006

# ENGLISH ABSTRACT

## Part I: Synthetic Studies on the Teleocidin Alkaloids

The first stereocontrolled formation of the characteristic all carbon quaternary centre of lyngbyatoxin A (**1.1**) is described. Indole (**3.78**), an advanced intermediate in a projected enantioselective total synthesis of lyngbyatoxin A (**1.1**), was prepared from allylic alcohol (**3.29**) over 9 steps in 13% yield and >95% *ee*, key transformation being the enantiospecific rearrangement of vinyl epoxide (**3.41**), formylation of silyl ether (**3.73**) *via* chemo- and regioselective halogen lithium exchange, and the Hemetsberger-Knittel reaction of azide (**3.74**).

In connection with studies towards the teleocidin B alkaloids (**1.3**) to (**1.6**), the first example of an intramolecular Heck reaction, that despite having the possibility for a 6-exo-trig path occurs exclusively to afford the 5-endo-trig cyclized product, is described. Indole (**5.7a**) was obtained in 3 steps in 67% yield from *p*-hydroxybenzaldehyde, the key step being the regioselective aromatic Claisen rearrangement of indole (**5.3**). The intramolecular Heck reaction of triflate (**5.7e**) is promoted only by bidentate phosphine ligands, and it affords indole (**5.18**) as the sole product in high yield (up to 94%).

## Part II: Catalytic Asymmetric Reactions of Enecarbamates with α,α'-Dicarbonyl Compounds

Catalytic asymmetric addition reactions of enecarbamates (*e.g.*, (**1.37**)) to ethyl glyoxylate using a catalyst derived from $CuClO_4 \cdot 4CH_4CN$ and a $C_2$-symmetric diimine ligand (*e.g.*, (**3.u**)) were developed. The *β*-hydroxy ketone adducts (*e.g.*, (**4.14**)), obtained by *in situ* acidic hydrolysis of the intermediate 1,3-hydroxy amines, are formed in good yield (>90%) and high enantiomeric excess (up to 97%). A concerted aza-ene mechanism for the addition reaction is proposed.

In the presence of a novel catalyst, generated from $Ni(OTf)_2$ and the $C_2$-symmetric diamine ligand (**3.d**), enecarbamates (*e.g.*, (**1.37**)) react with *α,α'*-diketones (*e.g.*, butane-2,3-dione) to afford, after *in situ* acidic hydrolysis, *tert*-alcohols (*e.g.*, (**4.41**)) in high yield (94%) and good optical purity (up to 84% *ee*). This process displays a strong positive non-liner effect.

## Part III: A Transannular Mannich Approach to Polycyclic Alkaloids: Synthetic Studies on the Cylindricine Alkaloids

A transannular Mannich approach to the cylindricine alkaloids (**3.1a**) to (**3.1k**) was investigated. Macrocycle diketone (**5.78**), which contains the basic skeleton of the proposed macrocycle precursor for the cylindricines (**2.12**), was prepared from cycloheptanone in 7 steps and 26% yield, key transformations being the Miyaura-Suzuki cross coupling reaction of bromocycloheptene (**5.67**) and *N*-Boc allyl amine (**5.75**), the formation of a 8-membered ring by an intramolecular displacement reaction, and the ring-enlargement reaction of [7,8]-bicyclic carbamate (**5.77**). Attempts to induce the desired transannular Mannich in macrocycle diketone (**5.78**) under acidic conditions resulted in the isolation of the dienol salt (**5.79**).

# ABSTRAKT


## 1. Del: Syntetiske Studier af Teleocidin Alkaloiderne

Den første stereokontrollerede dannelse af det karakteristiske kvaternære fuldt kul-substituerede caron atom i lyngbyatoxin A (**1.1**) er beskrevet. Indol (**3.78**) et sent intermediat i en planlagt enantioselektiv totalsyntese af lyngbyatoxin A (**1.1**) blev fremstillet ud fra den allyliske alcohol (**3.29**) over 9 trin i et samlet udbytte på 13% med en optisk renhed på >95% *ee*. Nøgletrinnene var en enantiospecifik omlejring af det vinyliske epoxid (**3.41**), en formylering af silyletheren (**3.73**) *via* kemo- og regioselektiv halogen lithium udveksling samt en Hemetsberger-Knittel reaktion på azidet (**3.74**).

I forbindelse med studierne mod teleocidin B alkaloiderne (**1.3**) to (**1.6**) observeredes det første eksempel på en intramolekylær Heck reaktion, som på trods af muligheden for en 6-exo-trig reaktionsvej, udelukkende giver anledning til dannelse af et 5-endo-trig afledt produkt. Indol (**5.7a**) blev fremstillet over 3 trin fra p-hydroxybenzaldehyd i et godt udbytte (67%). Nøgletrinnet var en regioselektiv aromatisk Claisen-omlejring af indol (**5.3**). Den intramolekylære Heck reaktion af triflat (**5.7e**) forløb kun med bidentate phosphinligander og gav udelukkende indol (**5.18**) i højt udbytte (op til 94%).

## 2. Del: Katalytiske Asymmetriske Reaktioner med Ene-Carbamater og α,α'-Dicarbonyl Forbindelser

Katalytiske asymmetriske additionsreaktioner med enecarbamater (*e.g.*, (**1.37**)) til ethylglyoxylat blev udviklet med en katalysator afledt fra $CuClO_4 \cdot 4CH_4CN$ og en $C_2$-symmetrisk diiiminligand (*e.g.*, (**3.u**)). Reaktionen førte til dannelse af *β*-hydroxyketoner (*e.g.*, (**4.14**)) efter *in situ* sur vandig hydrolyse af de intermediære 1,3-hydroxyaminer i højt udbytte (>90%) med høj optisk renhed (op til 97% *ee*). En ét trins aze-ene mekanisme er foreslået for denne reaktion.

Det er endvidere fundet, at enecarbamater (*e.g.*, (**1.37**)) reagerer i tilstedeværelse af en ny katalysator afledt fra $Ni(OTf)_2$ og den $C_2$-symmetriske diamineligand (**3.d**) med *α,α'*-diketoner (*e.g.*, butane-2,3-dion) under dannelse af tertiære alkoholer (*e.g.*, (**4.41**)) in højt udbytte (94%) og moderat-til-god optisk renhed (op til 84% *ee*) efter *in situ* sur hydrolyse. Denne process udviser en stærk positive ikke-lineær effekt.

## 3. Del: En Transannulær Mannich Syntesevej til Polycykliske Alkaloider: Syntesestudier mod Cylindricin Alkaloiderne

En transannulær Mannich strategy til syntese af cylindricin alkaloiderne (**3.1a**) til (**3.1k**) har været undersøgt. Den makrocykliske diketon (**5.78**), som indeholder det basale carbonskelet til dannelse af nøgleintermediatet i syntesen af cylindricinerne (**2.12**), blev fremstillet fra cycloheptanon over 7 trin i et samlet udbytte på 26%. De vigtigste trin var en Miyaura-Suzuki krydskobling af bromocyclohepten (**5.67**) og *N*-Boc allyl amine (**5.75**), dannelsen af en 8-ledet ring via en intramolekulær displaceringsreaktion, samt en ring-udvidelsesreaktion på det [7,8]-bicykliske carbamat (**5.77**). Forsøg på at få den ønskede transannulær Mannich til at forløbe med den makrocykliske diketon (**5.78**) under sure betingelser resulterede i dannelse af det tilsvarende dienol salt (**5.79**).

# LIST of PUBLICATIONS

At the time of submission of the present thesis, the PhD study has resulted in the following list of publications, which are included in Appendix I.

(1) **Vital, P.**; Tanner, D. "Efficient and Highly Enantioselective Formation of the All-Carbon Quaternary Stereocentre of Lyngbyatoxin A", *Org. Biomol. Chem.* **2006**, *4*, 4292.

(2) **Vital, P.**; Norrby, P.-O.; Tanner, D. "An Intramolecular Heck Reaction that Prefers a 5-*endo* to a 6-*exo-trig* Cylization Pathway", *Synlett* **2006**, 3140-3144.

(3) Fossey, J. S.; Matsubara, R.; **Vital, P.**; Kobayashi, S. "A $C_2$-Symmetric Nickel Diamine Complex as an Asymmetric Catalyst for Enecarbamate additions to Butane-2,3-dione", *Org. Biomol. Chem.* **2005**, *3*, 2910-2913.

(4) Matsubara, R.; **Vital, P.**; Nakamura, Y.; Kiyohara, H.; Kobayashi, S. " Highly Diastereo- and Enantioselecetive Reactions of Enecarbamates with an Aldeyhde", *Tetrahedron* **2004**, *60*, 9769-9784.

# LIST of ABBREVIATIONS

| | |
|---|---|
| $\alpha$ | optical Rotation |
| δ | chemical Shift |
| Ac | acetyl |
| All | allyl |
| Ar | aryl |
| aq. | aqueous |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| Bn | benzyl |
| Boc | *tert*-butylcarbonly |
| bp | boiling Point |
| br | broad (spectral) |
| Bu | butyl |
| BuLi or $^{n}$BuLi | *n*-butyllithium |
| $^{t}$BuLi | *tert*-butyllithium |
| $^{t}$BuOK | potassium *tert*-butoxide |
| Bz | benzoyl |
| CAN | cerium(IV) ammonium nitrate |
| Calcd | calculated |
| cat. | catalytic |
| Cbz | benzyloxycarbonyl |
| $cm^{-1}$ | wavenumber(s) |
| conc | concentrated |
| CSA | 10-Camphorsulphonic acid |
| D, L | dextrorotatory, levorotatory |
| d | doublet (spectral) |
| DAG | diacylglycerol |
| dba | dibenzylideneacetone |
| DDQ | *N,N'*-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAD | diethyl azodicarboxylate |
| *de* | diastereomeric excess |
| DET | diethyl tartrate |
| DIAD | diisopropyl azodicarboxylate |
| Dibal | diisopropylaluminum hydride |
| DIPT | diisopropyl tartrate |
| DMAP | 4-dimethylaminopyridine |

| | |
|---|---|
| DMF | dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMS | dimethyl sulfide |
| DMSO | dimethyl sulfoxide |
| DPPA | diphenylphosphoryl azide |
| dppf | 1,1'-bis(diphenylphosphino)ferrocene |
| *dr* | diastereomeric ratio |
| *E, Z* | Entgegen (German, "opposite"), Zusammen (German, "together") |
| EDC or EDCI | *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide |
| *ee* | enantiomeric excess |
| EI | electron impact |
| Et | Ethyl |
| $Et_2O$ | diethyl ether |
| equiv | equivalent(s) |
| FG | functional group(s) |
| FGI | functional group interconversion |
| g | gram(s) |
| h | hour(s) |
| *hv* | light |
| HMDS | hexamethyldisilazane |
| HPLC | high performance liquid chromatography |
| HWE | Horner-Wadsworth-Emmons |
| Hz | Hertz |
| IAHR | intramolecular asymmetric Heck reaction |
| ILV | indolactam V |
| imid | imidazole |
| IMM | intramolecular Mannich |
| IMDA | intramolecular Diels-Alder |
| IR | Infrared |
| *J* | coupling constant |
| KHMDS | potassium hexamethyldisilazide |
| K | Kelvin(s) |
| L, L* | liter; ligand, chiral ligand |
| LA | Lewis acid |
| LDA | lithium diisopropylamide |
| LD | lethal dose |
| lit. | literature |
| HRMS | high resolution mass spectra |

| | |
|---|---|
| LRMS | low resolution mass spectra |
| m | multiplet (spectral) |
| M | metal, Molar (moles *per* liter) |
| $M^+$ | parent molecular ion |
| *m/z* | mass-to-charge-ratio |
| MM | molecular mechanics |
| MCPBA | *m*-chloroperoxybenzoic Acid |
| Me | methyl |
| Met | methionine |
| MHz | Megahertz |
| mL | milliliter |
| mM | millimolar (millimoles *per* liter) |
| mmol | millimole(s) |
| mol | mole(s) |
| Mp | melting point |
| MS | mass spectrometry; molecular sieves |
| Ms | mesyl |
| *n*-, *i*-, *t*- | *normal*-, *iso*-, *tert*- |
| Naph | naphthyl |
| ni | not isolated |
| NLE | non-linear effects |
| NMR | nuclear magnetic resonance |
| NMM | *N*-methyl morpholine |
| *o*-, *m*-, *p*- | *ortho*-, *meta*-, *para*- |
| PG | protecting gropu |
| $PPh_3$ | triphenylphosphine |
| Ph | phenyl |
| ppm | part(s) *per* million |
| PMB | *p*-methoxybenzyl |
| PKC | protein kinase C |
| Piv | pivaloyl |
| PTLC | preparative thin layer chromatography |
| q | quartet (spectral) |
| quint | quintet (spectral) |
| *R*, *S* | *Rectus* (Latin, “right”), *Sinister* (Latin, “left”) |
| *rac* | racemic |
| RCM | ring closing metathesis |
| Red-Al | sodium bis(2-methoxyethoxy)aluminium Hydride |

| | |
|---|---|
| Ref. | reference |
| Rf | retention factor (for TLC) |
| rt | room temperature |
| s | singlet (spectral) |
| SAE | Sharpless asymmetric epoxidation |
| sat. | saturated |
| SEM | 2-(trimethylsilyl)ethoxymethyl |
| SM | starting material(s) |
| t | triplet (spectral) |
| TFA | trifluoroacetic acid |
| TADA | transannular Diels Alder |
| TAM | transannular Mannich |
| TBAF | tetrabutylammonium fluoride |
| TBDMS | *tert*-butyldimethylsilyl |
| TBDMSOTf | trimethylsilyl trifluoromethanesulfonate |
| Tf | trifluoromethanesulfonyl |
| $Tf_2O$ | triflic anyhdride |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMEDA | *N*,*N*,*N'*,*N'*-tetramethylethylenediamine |
| TMS | trimethylsilyl |
| tr | retention time (chromatography) |
| Trp | tryptophan |
| Ts | tosyl |
| TS | transition state |
| Val | valine |
| X | halogen; generic functional group |

# Part I

Synthetic Studies on the Teleocidin Alkaloids

Part I

# CHAPTER 1
# The Teleocidin Alkaloids - An Overview

## 1.1 - Isolation and Structure

"Teleocidin", isolated from the mycelia of the soil bacteria *Streptomyces mediocidicus* by Takashima and Sakai in 1960, has a strong skin-irritating action and shows a highly potent toxicity against aquatic animals.[1.1] In 1983, Fujuki and co-workers disclosed that "teleocidin" was in fact a mixture of closely related compounds, namely two teleocidin A isomers, teleocidins A-1 (**1.1**) and A-2 (**1.2**), and four teleocidin B isomers, teleocidins B-1 (**1.3**) to B-4 (**1.6**), according to their order of elution on reverse phase HPLC.[1.2] Meanwhile, in 1979, while studying the origin of a severe dermatitis condition known as swimmers' itch, Moore and co-workers isolated lyngbyatoxin A (**1.1**), a highly inflammatory and vesicatory substance.[1.3] Lyngbyatoxin A was obtained from a Hawaiian shallow-water variety of the blue-green algae[1.4] *Lyngbya majuscula* Gomont. More recently, in 1986, the Fujiki group unveiled that teleocidin A-1 is identical to lyngbyatoxin A.[1.5]

Based on extensive chemical and spectroscopic studies and X-ray crystallographic analysis, the structures of all teleocidins have been unambiguously established,[1.1,1.3] including their absolute configuration.[1.5,1.6] These efforts showed that the teleocidins are indole alkaloids containing a highly functionalized 9-membered lactam bridging the indole 3- and 4-positions. In addition, each member of the teleocidin family has a distinctive complex monoterpenoid moiety: whereas the teleocidins A are characterized by a linalyl (*i.e.*, 1,5-dimethyl-1-vinyl-4-hexenyl) side chain at the 7-

[1.1] (a) Takashima, M.; Sakai, H. *Bull. Agric. Chem. Soc. Jpn.* **1960**, *24*, 647. (b) Takashima, M.; Sakai, H. *Bull. Agric. Chem. Soc. Jpn.* **1960**, *24*, 652. (c) Takashima, M.; Sakai, H; Arima, K. *Agric. Biol. Chem.* **1962**, *26*, 660. (d) Takashima, M.; Sakai, H; Arima, K. *Agric. Biol. Chem.* **1962**, *26*, 669.

[1.2] Fujiki, H.; Sugimura, T. *Cancer Surveys* **1983**, *2*, 539.

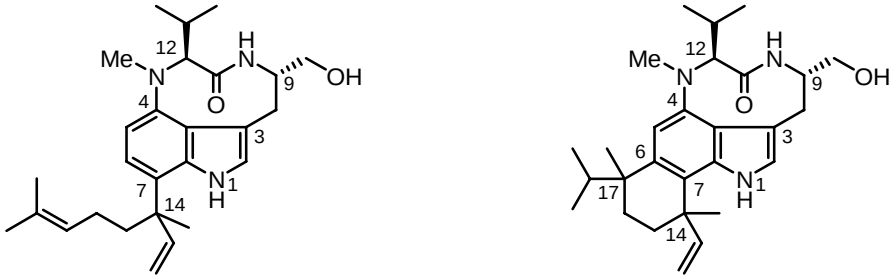
[1.3] Cardellina II, J. H.; Marner, F.-J.; Moore, R. E. *Science* **1979**, *204*, 193.

[1.4] "Blue-green algae", "cyanobacteria" or "seaweed" are some of the various names used in the literature to refer to cyanophytes. Cyanophytes can loosely be defined as prokaryotic, chlorophyll-containing organisms which have no true roots, stems or leaves and thus are neither bacteria nor algae.

[1.5] Sakai, S.; Hitotsuyanagi, Y.; Aimi, N.; Fujiki, H.; Suganuma, M.; Sugimura, T.; Endo, Y.; Shudo, K. *Tetrahedron Lett.* **1986**, *27*, 5219.

[1.6] (a) Hitotsuyanagi, Y.; Fujiki, H.; Suganuma, M.; Aimi, N.; Sakai, S.; Endo, Y.; Shudo, K.; Sugimura, T. *Chem. Pharm. Bull.* **1984**, *32*, 4233. (b) Sakai, S.; Aimi, N.; Yamaguchi, K.; Hitotsuyanagi, Y.; Watanabe, C.; Yokose, K.; Koyama, Y.; Shudo, K.; Itai, A. *Chem. Pharm. Bull.* **1984**, *32*, 354.

position of the indole nucleus, the teleocidins B contain a 6-membered carbocyclic framework bridging the 6- and 7-positions of the indole nucleus (Figure 1.1).




**1.1**: Lyngbyatoxin A (aka Teleocidin A-1) (14*R*)
**1.2**: Teleocidin A-2 (14*S*)

**1.3**: Teleocidin B-1 (14*R*,17*S*)
**1.4**: Teleocidin B-2 (14*S*,17*R*)
**1.5**: Teleocidin B-3 (14*S*,17*S*)
**1.6**: Teleocidin B-4 (14*R*,17*R*)

**Figure 1.1** The teleocidin alkaloids.

The teleocidins are structurally related to several other alkaloids which also contain the (-)-indolactam V (ILV)[1.7] (**1.7**) core and hence are often referred to as the indolactam alkaloids. Other members of this family include pendolmycin (**1.8**),[1.8] cytoblastin (**1.9**),[1.9] blastmycetin F (**1.10**)[1.10] and the olivoretins (*e.g.*, olivoretin C (**1.11**) and olivoretin E (**1.12**)),[1.11] (Figure 1.2).

[1.7] Irie, K.; Hirota, M.; Hagiwara, N.; Koshimidzu, K.; Hayashi, H.; Murao, S.; Tokuda, H.; Ito, Y. *Agric. Biol. Chem.* **1984**, *48*, 1269.
[1.8] Yamashita, T.; Imoto, M.; Isshiki, K.; Sawa, T.; Naganawa, H.; Kurasawa, S.; Shu, B.-Q.; Umezawa, K. *J. Nat. Prod.* **1988**, *51*, 1184.
[1.9] (a) Kumagai, H.; Iijima, M; Dobashi, K.; Naganawa, H.; Sawa, T.; Hamada, M.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1994**, *44*, 1029.
[1.10] Irie, K.; Kajiyama, S.-I.; Okuno, S.; Kondo, M.; Koshimizu, K. *J. Nat. Prod.* **1994**, *57*, 363.
[1.11] (a) Sakai, S.; Aimi, N.; Yamaguchi, K.; Hitotsuyanagi, Y.; Watanabe, C.; Yokose, K.; Koyama, Y.; Shudo, K.; Itai, A. *Chem. Pharm. Bull.* **1984**, *32*, 354. (b) Hitotsuyanagi, Y.; Yamaguchi, K., Ogata, K.; Aimi, N.; Sakai, S.; Koyama, Y.; Endo, Y.; Shudo, K.; Itai, A.; Iitaka, Y.; *Chem. Pharm. Bull.* **1984**, *32*, 3774. (c) Sakai, S.; Hitotsuyanagi, Y.; Yamaguchi, K.; Aimi, N.; Ogata, K.; Kuramochi, T.; Seki, H.; Hara, R.; Fujiki, H.; Suganuma, M.; Sugimura, T.; Endo, Y.; Shudo, K.; Koyama, Y. *Chem. Pharm. Bull.* **1986**, *34*, 4883.

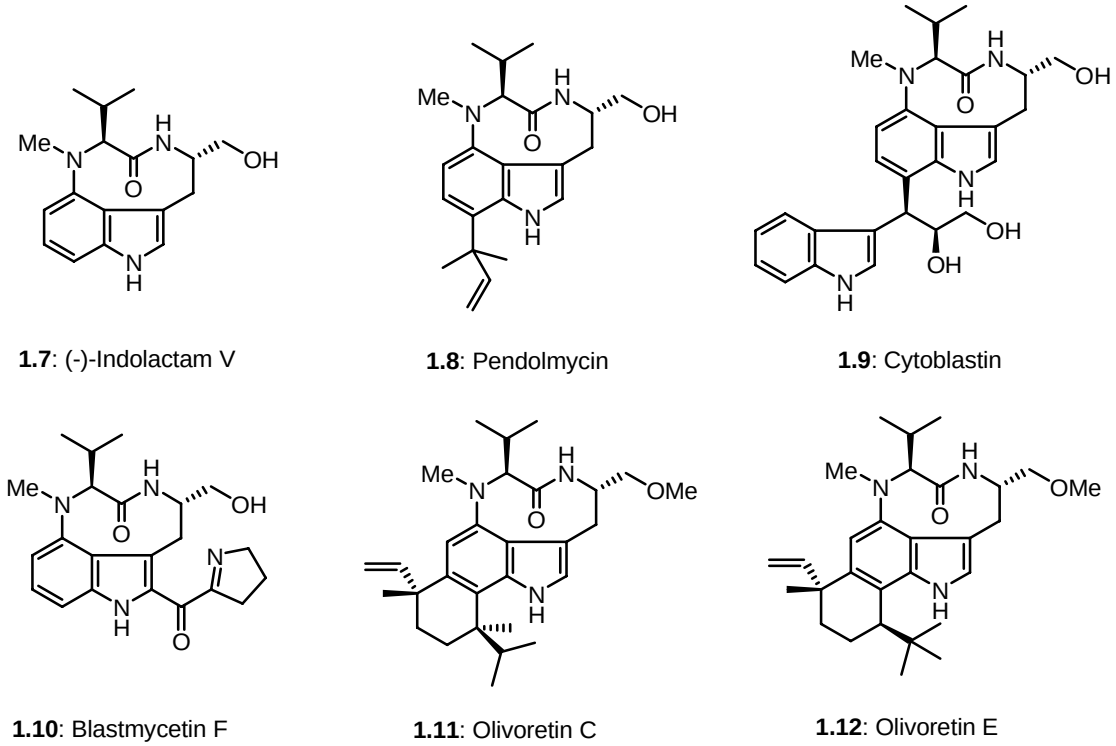
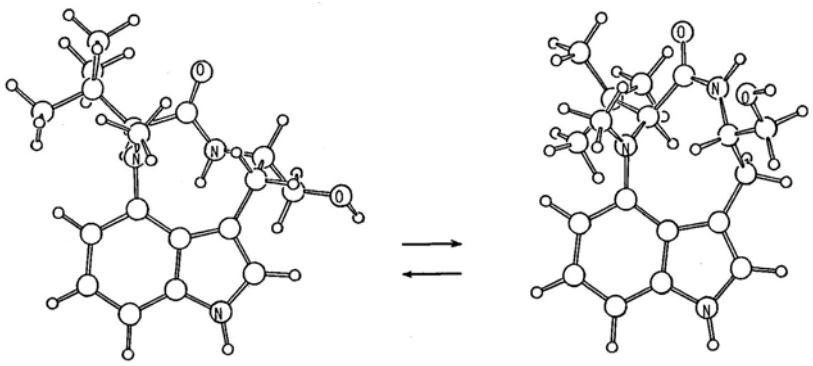



**Figure 1.2** Selected examples of indolactam alkaloids.

An important structural feature of the indolactam alkaloids with significant biological implications (*vide infra*, section 1.3) is that the nine-membered lactam ring present in this family of compounds exists in solution as an equilibrium between at least two stable conformational states.[1.12] The two conformers, often called twist (**1.13**) and sofa (**1.14**), are mainly characterized by a *cis* and a *trans* amide bond, respectively, as illustrated in Figure 1.3 for ILV.

[1.12] (a) Endo, Y.; Hasegawa, M.; Itai, A.; Shudo, K.; Tori, M.; Asakawa, Y.; Sakai, S. *Tetrahedron Lett.* **1985**, *26*, 1069. (b) Endo, Y.; Shudo, K.; Itai, A.; Hasegawa, M.; Sakai, S. *Tetrahedron* **1986**, *21*, 5905. (c) Kawai, T.; Ichinose, T.; Takeda, M.; Tomioka, N.; Endo, Y.; Yamaguchi, K.; Shudo, K.; Itai, A. *J. Org. Chem.* **1992**, *57*, 6150.



**1.13**: Sofa form **1.14**: Twist form

**Figure 1.3** Conformational equilibrium for ILV.

## 1.2 - Biosynthesis

The metabolic pathway leading to the teleocidins alkaloids has already been elucidated in considerable detail (Scheme 1.1).[1.13,1.14,1.15] Biosynthetic studies in *Streptomyces blastmyceticum* by Koshimidzu and co-workers showed that ILV (**1.7**) is the biosynthetic precursor of the teleocidins and that the ILV core is assembled from L-tryptophan (L-Trp), L-valine (L-Val) and L-methionine (L-Met).[1.13a] The first step in the biosynthesis of ILV is the formation of the *N*-methyl-L-valyl-L-tryptophanol (**1.15**). Activation of the 4-position of the indole ring of dipeptide (**1.15**), presumably *via* oxidation to epoxide (**1.16**), followed by subsequent cyclisation affords ILV (**1.7**).[1.14] As for the monoterpenoid side chain, studies in *Streptomyces blastmyceticum* by Irie and co-workers showed that it is derived from D-glucose *via* the non-mevalonate pathway.[1.15] The incorporation of the linalyl moiety into the 7-positon of ILV is proposed to proceed in two steps: initial prenylation of the indole nitrogen with geranyl pyrophosphate (GPP) (**1.17**) affords (**1.18**)[1.16] and a subsequent aza-Claisen-type rearrangement delivers the teleocidins A. Finally, methylation at C-17 followed by an intramolecular cyclization delivers the teleocidins B.[1.13b]

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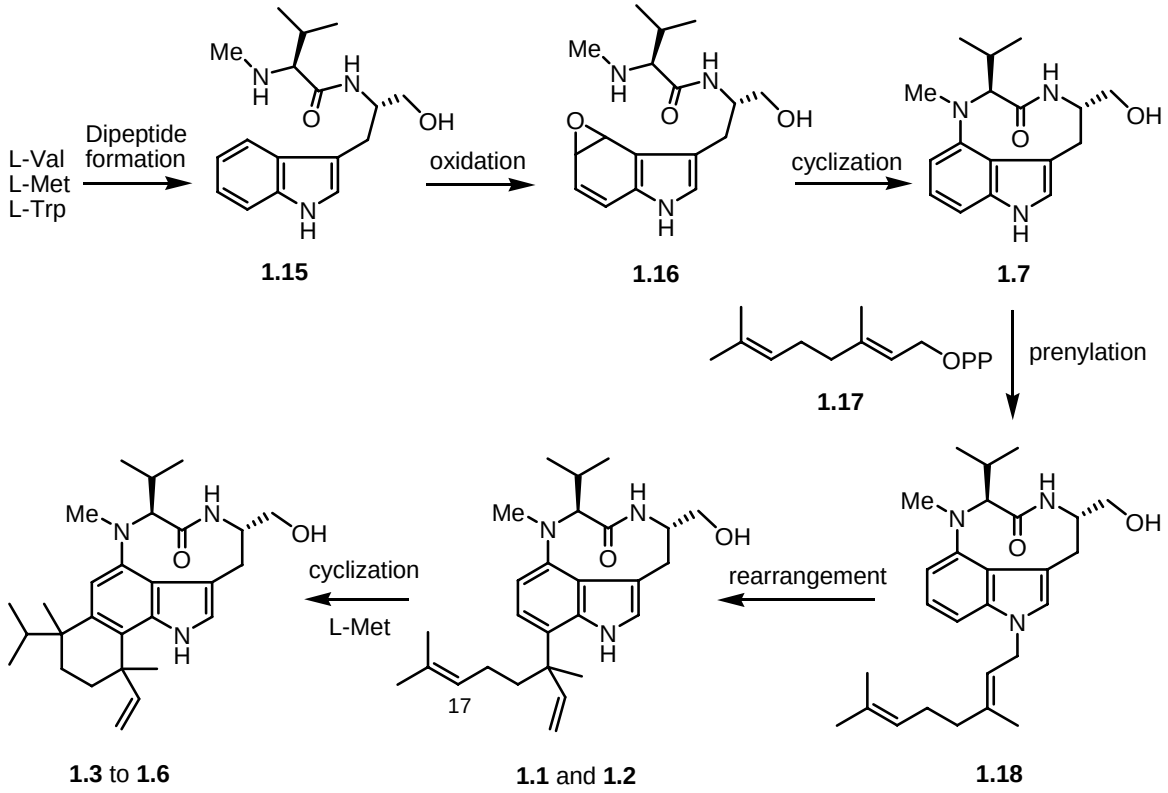
[1.13] (a) Irie, K.; Kajiyama, S.; Funaki, A.; Koshimidzu, K. *Tetrahedron Lett.* **1990**, *31*, 101. (b) Irie, K.; Kajiyama, S.; Funaki, A.; Koshimidzu, K. *Tetrahedron* **1990**, *46*, 2773.

[1.14] Edwards, D. J.; Gerwick, W. H. *J. Am. Chem. Soc.* **2004**, *126*, 11432.

[1.15] Irie, K.; Nakagawa, Y.; Tomimatsu, S.; Ohigashi, H. *Tetrahedron Lett.* **1998**, *39*, 7929.

[1.16] *N*-prenylated (**1.18**) is also an important intermediate in biosynthesis of the olivoretins alkaloids. See Ref. 1.13b.




**Scheme 1.1** Biosynthesis of the teleocidins.

## 1.3 - Biological Activity

Upon their isolation it was found that the teleocidins, besides being highly inflammatory and vesicatory agents, also possess significant toxicity.[1.1,1.3] Moore and co-workers found that the minimum lethal dose ($LD_{100}$) of lyngbyatoxin A in mice is about 0.3 $mgkg^{-1}$ (by intraperitoneal injection) and that this alkaloid was able to kill all bait fish within ½ h at a concentration in seawater of 0.15 $\mu gmL^{-1}$.[1.3] These values are comparable to those reported by the Hirata[1.17] and the Takashima[1.1d] groups for teleocidin B-4: the $LD_{50}$ in mice is 0.22 $mgkg^{-1}$ (by intravenous injection) and it causes the death of Japanese killifish within 1 h at a concentration of 0.01 $\mu gmL^{-1}$. Lyngbyatoxin A has also been linked to a human fatality due to consumption of sea turtle flesh whose diet presumably included *L. majuscula*.[1.18]

[1.17] Sakabe, N.; Harada, H.; Hirata, Y.; Tomiie, Y.; Nitta, I. *Tetrahedron Lett.* **1966**, 2523.
[1.18] Ito, E.; Satake, M.; Yasumoto, T. *Toxicon* **2002**, *40*, 551.

More recently, and of greater importance, it was disclosed that these alkaloids are potent tumor promoters and that they exert their biological activity by activating protein kinase C (PKC).[1.2,1.19,1.20] PKC is a complex phosphorylating serine/threonine enzyme system comprised of at least ten isoenzymes. The different isoenzymes play a specific role in the regulation of several essential cellular processes.[1.21,1.22,1.23] Therefore, the discovery of isoenzymes-selective activators and inhibitors of PKC is crucial to ascertaining the role of the individual isoenzymes in physiological processes and to manipulating their function.[1.24,1.25]

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[1.19] (a) Fujiki, H.; Mori, M.; Nakayasu, M.; Terada, M.; Sugimura, T.; Moore, R. E. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 3872. (b) Fujiki, H.; Suganuma, M.; Hakii, H.; Bartolini, G.; Moore, R. E.; Takayama, S.; Sugimura, T. *J. Cancer Res. Clin. Oncol.* **1984**, *108*, 174. (c) For a review see: Fujiki, H.; Sugimura, T. *Adv. Cancer Res.* **1987**, *49*, 223.

[1.20] For a review dealing with anticancer agents and tumor promoters derived from marine prokaryotes see: Moore, R. E. *Pure & Appl. Chem.* **1982**, *54*, 1919.

[1.21] (a) Newton, A. C. *Chem. Rev.* **2001**, *101*, 2353. (b) Stillman, B. *Science* **1996**, *274*, 1659. (c) Barinaga, M. *Science* **1997**, *278*, 1036. (d) Nishizuka, Y. *Science* **1992**, *258*, 607.

[1.22] Kishi, Y.; Rando, R. R. *Acc. Chem. Res.* **1998**, *31*, 163.

[1.23] According to the conditions required for activation (*i.e.*, cofactors), the PKC isoenzymes are subdivided in three groups[1.21a]: the conventional PKC (cPKCs) ($\alpha$, $\beta$I, $\beta$II, $\gamma$), the novel PKC (nPKCs) ($\delta$, $\varepsilon$, $\eta$, $\theta$) and the atypical PKC (aPKCs) ($\zeta$, $\lambda/\iota$). Regarding the primary structure of the PKC isoenzymes, a C-terminal moiety contains the kinase domain, which is common to all PKCs, whereas a N-terminal moiety contains the regulatory modules. The later possess two key functionalities: the pseudosubstrate and one or two membrane-targeting modules (the C1 domain which for cPKCs and nPKCs binds diacylglycerolds (DAGs) and the C2 domain which for cPKCs binds $Ca^{2+}$) (Figure 1.A).

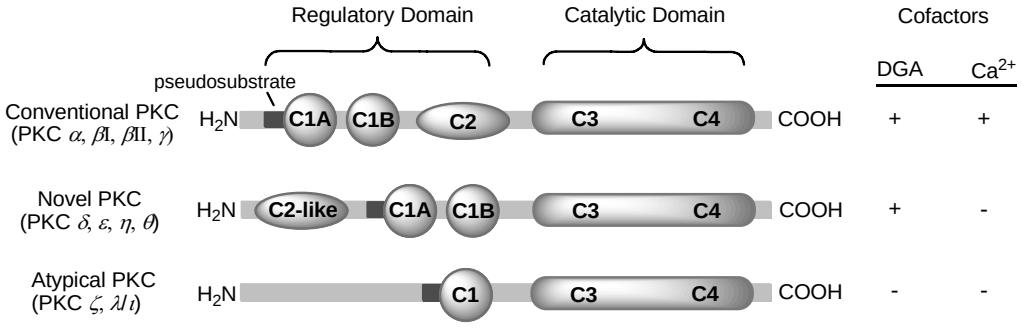
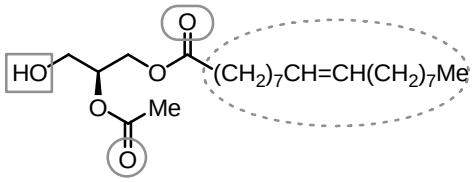



**Figure 1.A**: Primary structure of PKC isoenzymes showing the domain composition and co-factors.

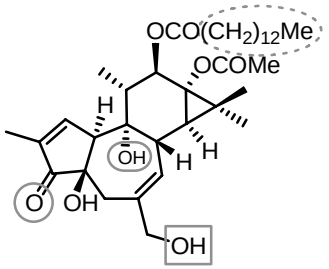
[1.24] Recent investigations suggested that the nPKCs are involved in mouse skin tumor promotion and that the C1B domains of these PKC isoenzymes are the main targets of tumor promoters.[1.25] Thus, the design of new agents with high selectivity for C1B domains of nPKCs is indispensable in elucidating the precise mechanism of skin-tumor promotion.

[1.25] (a) Lu, Z.; Hornia, A.; Jiang, Y. W.; Zang, Q.; Ohno, S.; Foster, D. A. *Mol. Cell. Biol.* **1997**, *17*, 3418. (b) Reddig, P. J.; Dreckschmidt, N. E.; Ahrens, H.; Simsiman, R.; Tseng, C. P.; Zou, J.;

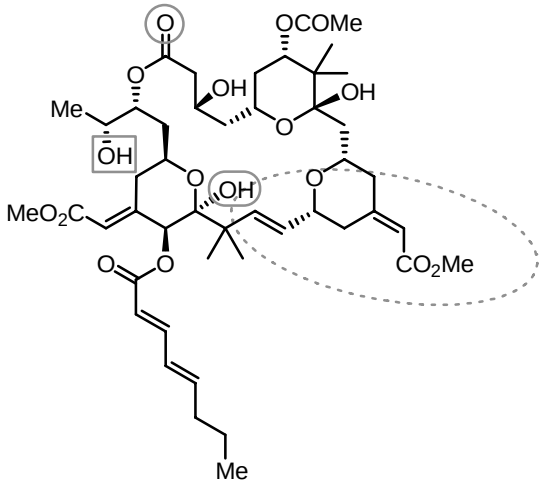
Physiologically, PKC is activated by (*S*)-1,2-diacylglycerols (DGAs) (*e.g.*, (**1.19)**).[1.23] The role of the DAGs can, however, be mimicked by various, structurally diverse, natural products, namely the phorbol esters (*e.g.*, (**1.20)**), the bryostatins (*e.g.*, (**1.21**)) and the indolactam alkaloids (*e.g.*, (**1.22**)) (Figure 1.4). Analysis of these compounds led Kishi to propose that, regarding the activation of PKCs, the existence of three hydrophilic atoms separated by approximately 6 Å (three-point model), together with a hydrophobic moiety, constitute a possible pharmacophore.[1.22]



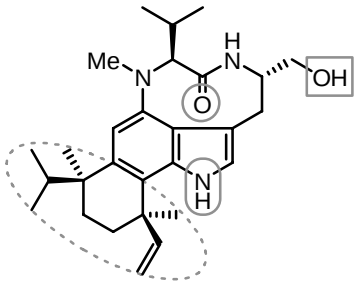

**1.19**: (*S*)-1-Oleoyl-2-acetylglycerol




**1.20**: 12-O-Tetradecanoylphorbol-13-O-acetate (TPA)




**1.21**: Bryostatin 1




**1.22**: Teleocidin B-4

**Figure 1.4** Structure of a representative DAG (**1.19**) and various tumor promoters ((**1.20**) to (**1.22**)); corresponding moieties in pharmacophores are indicated by the same outlining feature.

Oberley, T. D.; Verma, A. K. *Cancer Res.* **1999**, *59*, 5710. (c) Reddig, P. J.; Dreckschmidt, N. E.; Bourguignon, S. E.; Oberley, T. D.; Verma, A. K. *Cancer Res.* **2000**, *60*, 595. (d) Chida, K.; Hara, T.; Hirai, T.; Konoshi, C.; Nakamura, K.; Nakao, K.; Aiba, A.; Katsuki, M.; Kuroki, T. *Cancer Res.* **2003**, *63*, 2404.

With respect to the indolactam alkaloids, Fujiki and co-workers showed that the minimum structure for biological activity corresponds to (-)-ILV (**1.7**)[1.26] and more recently, Irie and co-workers disclosed that (-)-IVL shows a biding preference for C1B domains over C1A domains of nPKCs.[1.27] The hydrophobic moiety on the indole ring of the teleocidins plays a critical role in increasing the biological potency: the activity of teleocidin B-5 (**1.6**) in terms of the biding affinity to PKC and growth inhibition of HL-60 cells is 100-500 times higher than that of (-)-ILV, which lacks the hydrophobic moiey.[1.28] However, there is not a great deal of (stereo)specificity directed towards the nature of this hydrophobic moiety as the teleocidins B, which are stereochemical isomers of the C-14 and C-17 positions of the terpenoid side chain, and their open-chain analogues, the teleocidins A, exhibit similar biological activity.[1.29] Furthermore, the terpenoid substituents of the teleocidins can be replaced by a simple linear alkyl group without loss of activity.[1.30]

The biological activity of the indolactam alkaloids shows an interesting dependence on conformation. As mentioned before all the teleocidins exist in an equilibrium of two conformational states, the twist and sofa forms (*vide supra*, Section 1.1).[1.12] The Erie group disclosed that, in the indolactam family, the biologically active form is (closer) to the twist conformer.[1.31c,1.31e]

Aiming at finding teleocidin-analogues that were synthetically more accessible and/or isoenzymes selective, different analogues were synthesized and tested.[1.12,1.31] A

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[1.26] Fujiki, H.; Suganuma, M.; Hakii, H.; Nakayasu, M.; Endo, Y.; Shudo, K.; Irie, K.; Koshimizu, K.; Sugimura, T. *Proc. Jpn. Acad. Ser. B* **1985**, *61*, 45.

[1.27] Masuda, A.; Irie, K.; Nakagawa, Y.; Ohigashi, H. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1615.

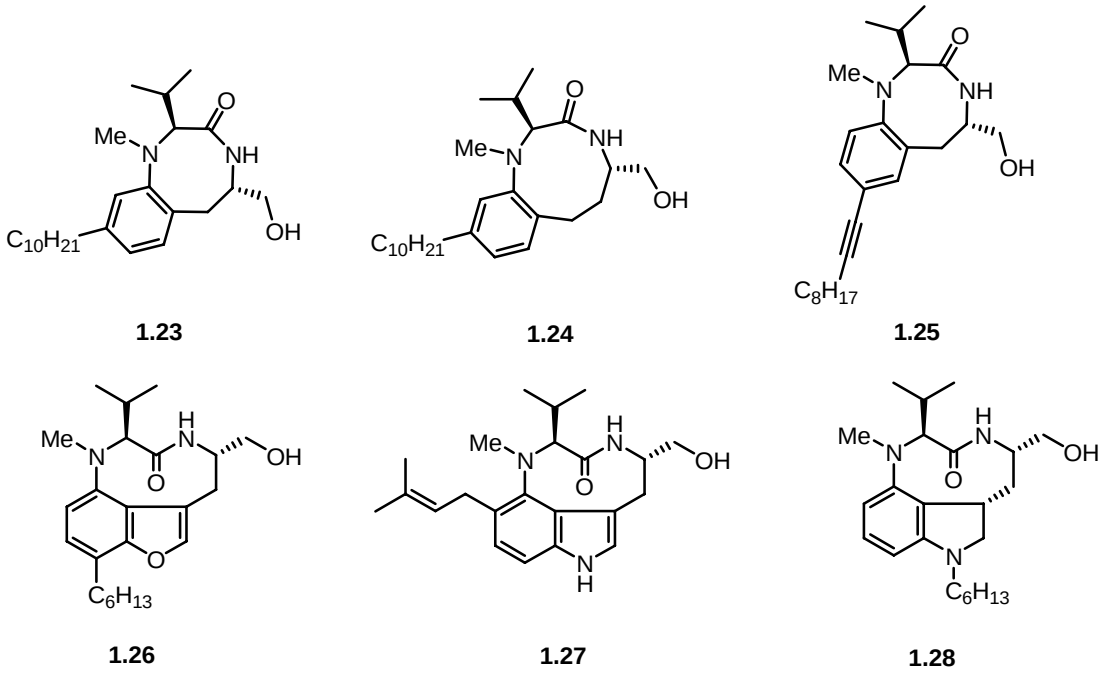
[1.28] Fujiki, H.; Suganuma, M.; Nakayasu, M.; Tahira, T.; Endo, Y.; Shudo, K. *Jpn. J. Cancer Res. (Gann)* **1984**, *75*, 866.

[1.29] Fujiki, H.; Suganuma, M.; Ninomiya, M.; Yoshizawa, S.; Yamashita, K.; Takayama, S.; Hitotsuyanagi, Y.; Sakai, S.-I.; Shudo, K.; Sugimura, T. *Cancer Res.* **1988**, *48*, 4211.

[1.30] (a) Irie, K.; Hayashi, H.; Arai, M.; Koshimizu, K. *Agric. Biol. Chem.* **1986**, *50*, 2679. (b) Endo, Y.; Sato, Y.; Shudo, K. *Tetrahedron Lett.* **1987**, *43*, 2241.

[1.31] (a) Endo, Y.; Ohno, M.; Hirano, M.; Shudo, K. *J. Am. Chem. Soc.* **1996**, *118*, 1841. (b) Endo, Y.; Yamaguchi, M.; Hirano, M.; Shudo, K. *Chem. Pharm. Bull.* **1996**, *44*, 1138. (c) Kozikowski, A. P.; Ma, D.; Pang, Y.; Shum, P.; Likic, V.; Mishra, P. K.; Macura, A.; Basu, J. S.; Lazo, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 3957. (d) Kozikowski, A. P.; Ma, D.; Du, L.; Lewin, N. E. Blumberg, *J. Am. Chem. Soc.* **1995**, *117*, 6666. (e) Irie, K.; Isaka, T.; Iwata, Y.; Yanai, Y.; Nakamura, Y.; Koizumi, F.; Ohigashi, H.; Wender, P. A. Satomi, Y.; Nishino, H. *J. Am. Chem. Soc.* **1996**, *118*, 10733. (f) Ma, D.; Tang, W.; Kozikowski, A. P.; Lewin, N. E.; Blumberg, P. M. *J. Org. Chem.* **1999**, *64*, 6366. (g) Wei, Z.-L.; Sakamuri, S.; Petukhov, P. A.; George, C.; Lewin, N. E.; Blumberg, P. M.; Kozikowski, A. P.

representative selection is shown in Figure 1.5. Accordingly, the Endo group reported that the benzo-derivative (**1.23**), containing a 8-membered lactam and which mimics the indolactam twist conformation, was a potent PKC activator,[1.31a] On the other hand, Kozikowski disclosed that the analogue (**1.24**) that mimics the sofa conformation of the indole alkaloids was virtually incapable of activating PKC: whereas (**1.23**) caused growth inhibition and differentiation of HL-60 cells at a concentration of $10^{-8}$ M, (**1.24**) proved to be inactive at concentrations bellow $10^{-5}$ M.[1.31a,1.31c] The nature of the side chains appendages can alter isoform selectivity (*e.g.*, the analogue (**1.25**) exhibited improved isoenzymes selectivity in comparison with its saturated side-chain counter part).[1.32] By replacing the indole backbone with a benzofuran, as in (**1.26**), Kozikowski and co-workers showed that the indole nitrogen has a (modest) role in the isoenzymes selectivity but only plays a supporting role in the interaction with the PKC.[1.31d] Interestingly, Irie and co-workers recently reported that analogues (**1.27)** and (**1.28**) with a sofa-like conformation show significant selectivity for nPKC isoenzymes.[1.27,1.31h]




**1.23** **1.24** **1.25**

**1.26** **1.27** **1.28**

**Figure 1.5** Examples of teleocidin-analogues.

*Org. Lett.* **2002**, *4*, 2169. (h) Nakagawa, Y.; Irie, K.; Komiya, Y.; Ohigashi, H.; Tsuda, K. *Tetrahedron* **2004**, *60*, 7077.

[1.32] Kosikowski, A. P.; Wang, S.; Ma, D.; Yao, J.; Ahmad, S.; Glazer, R. I.; Bogi, K.; Acs, P.; Modarres, S.; Lewin, N. E.; Blumberg, P. M. *J. Med. Chem.* **1997**, *40*, 1316.

## 1.4 - Selected Total Synthesis of Indolactam Alkaloids

The unusual structure of the indolactam alkaloids, together with their interesting biological profile, has made them worthy targets for the organic synthetic community over the past years.[1.33,1.34,1.35,1.36] While several total syntheses of (-)-ILV (**1.7**) have been reported,[1.33] at the time of this writing there has only been published one total synthesis[1.34a-1.34c] and a formal total synthesis[1.34d] of the structurally more complex teleocidins A (**1.1**) and (**1.2**), and two total synthesis[1.35] of teleocidins B-3 (**1.5**) and B-4 (**1.6**). Total syntheses of pendolmycin (**1.8**)[1.34c] and cytoblastin (**1.9**) [1.36] have also been reported.

In the Natsume total synthesis of teleocidins A,[1.34a-c] B-3 and B-4,[1.35] the indole nucleus is accessed from a preformed pyrrole ring system by construction of the benzenoid aromatic ring (Scheme 1.2). For lyngbyatoxin A, [1.34a-c] the linalyl side chain is installed at an early stage in the synthetic sequence *via* the Grignard reaction of geranly bromide with the enantiomerically pure L-valine ketoamide pyrrole derivative (**1.30**), affording the tertiary alcohol (**1.32a**) as a diasteromeric mixture. Dehydration and conversion into the corresponding thioamide (**1.33a**) followed by a Bischler-Napieralski type cyclization produces the 7-alkyl 4-aminoindole (**1.34a**) as a mixture of epimers at C-14. After separation of the diastereoisomers, the indolic C-3 position was then functionalized *via* 3-bromo-2-hydroxyiminopropanoate. Reduction of the resulting oxime afforded a 1:1 inseparable mixture of diastereoisomeric amino esters (**1.35a**) at the newly installed chiral centre C-9. Finally, construction of the nine-membered lactam ring, achieved with DPPA, and separation of the corresponding diastereoisomers afforded lyngbyatoxin A (as well as teleocidin A-2). Alternatively,

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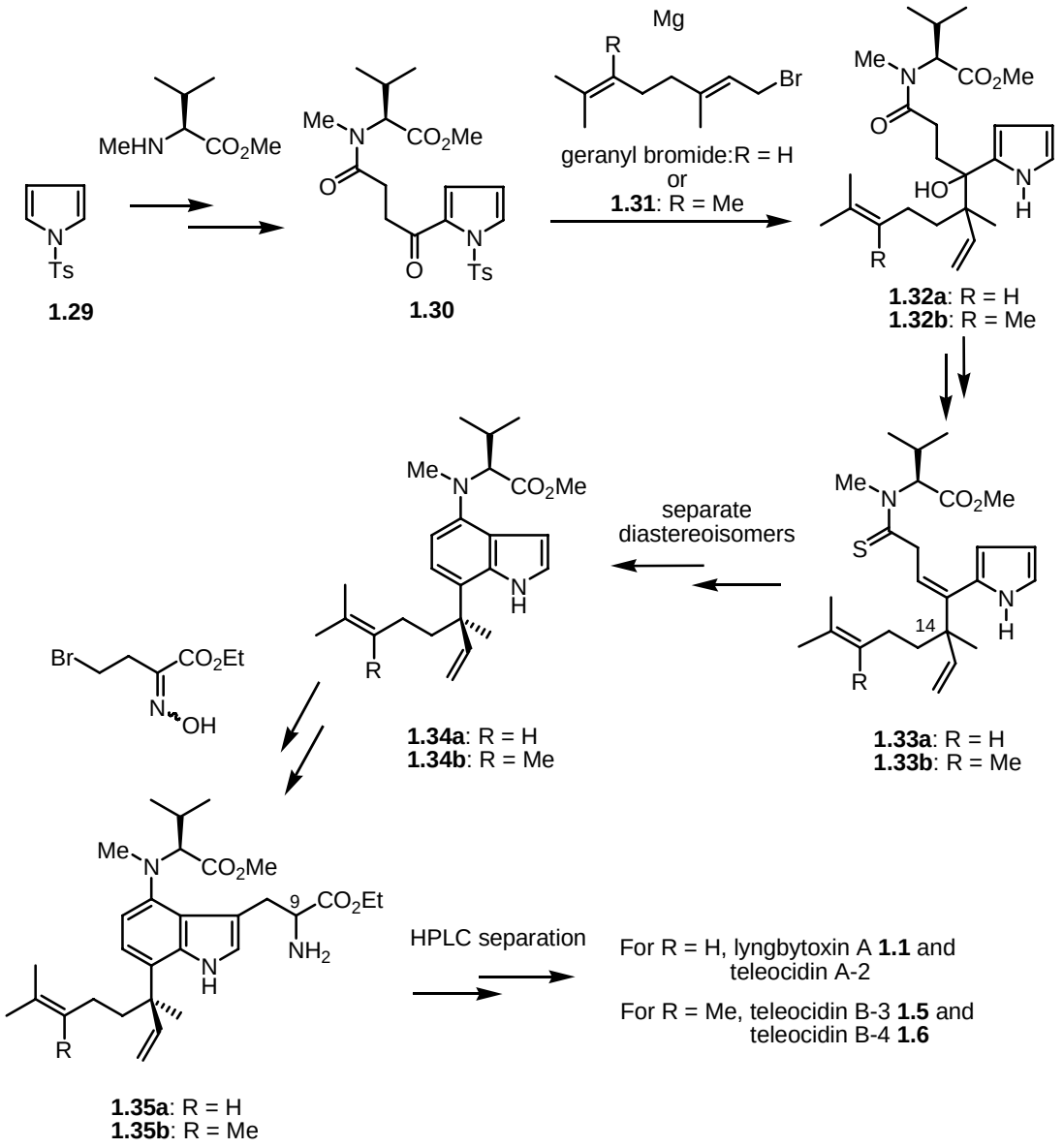
[1.33] For selected total synthesis of (-)-ILV (**1.7**) see: (a) Kogan, T. P.; Somers, T. C.; Venuti, M. C. *Tetrahedron* **1990**, *46*, 6623. (b) Nakatsuka, S.; Masuda, T.; Sakai, K.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 5735. (c) Mascal, M.; Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1988**, 589. (d) Quick, J.; Saha, B.; Driedger, P. E. *Tetrahedron Lett.* **1994**, *35*, 8549. (e) Endo, Y.; Shudo, K.; Itai, A.; Hasegawa, M.; Sakai, S. *Tetrahedron* **1986**, *42*, 5905.

[1.34] For total synthesis of the teleocidins A (**1.1**) and (**1.2**) see: (a) Muratake, H., Natsume, M. *Tetrahedron Lett.* **1987**, *28*, 2265. (b) Muratake, H., Natsume, M. *Tetrahedron.* **1991**, *47*, 8535. (c) Muratake, H., Natsume, M. *Tetrahedron* **1991**, *47*, 8545. (d) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1399.

[1.35] For total synthesis of teleocidins B-3 (**1.5**) and B-4 (**1.6**) see: (a) Nakatsuka, S.; Masuda, T.; Goto, T. *Tetrahedron Lett.* **1987**, *28*, 3671. (b) Okabe, K.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1989**, *37*, 563. (c) Okabe, K.; Muratake, H.; Natsume, M., *Tetrahedron* **1991**, *47*, 8559.

[1.36] For the total synthesis of cytoblastin (**1.9**) see: Moreno, O. A.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 8180.

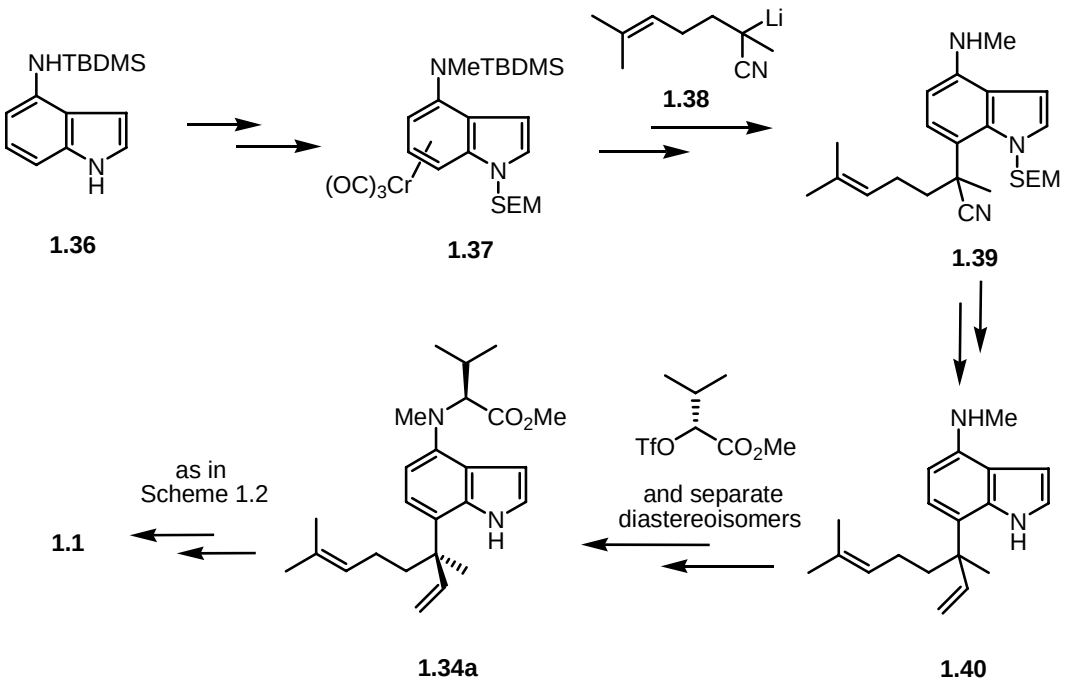
by starting with the homologue terpenoid moiety (**1.31**) and using the same sequence of steps plus a final acid-promoted intramolecular Friedel-Crafts cyclization, Natsume and co-workers also prepared teleocidins B-3 and B-4.[1.35]




**Scheme 1.2** Highlights of Natsume's total synthesis of the teleocidins A (**1.1**) and (**1.2**), B-3 (**1.5**) and B-4 (**1.6**).

Semmelhack and Rhee[1.34d] achieved a formal total synthesis of lyngbytoxin A in which a precursor of the linalyl side chain at C-7 is introduced as the nitrile-stabilized lithium anion (**1.38**) *via* nucleophilic attack onto the $Cr(CO)_3$ complex of the protected 4-amino indole (**1.37**) affording, after oxidation, indole (**1.39**). The L-valine

unit was introduced by means of a stereospecific displacement of the triflate of (*R*)-2-hydroxyvaleric acid methyl ester by the C-4 methylamino substituent in (**1.40**), thus obtaining the (*S*)-*N*-valylindole (**1.34a**), which has already been successfully converted into lyngbytoxin A (*vide supra*, Scheme 1.2) (Scheme 1.3).

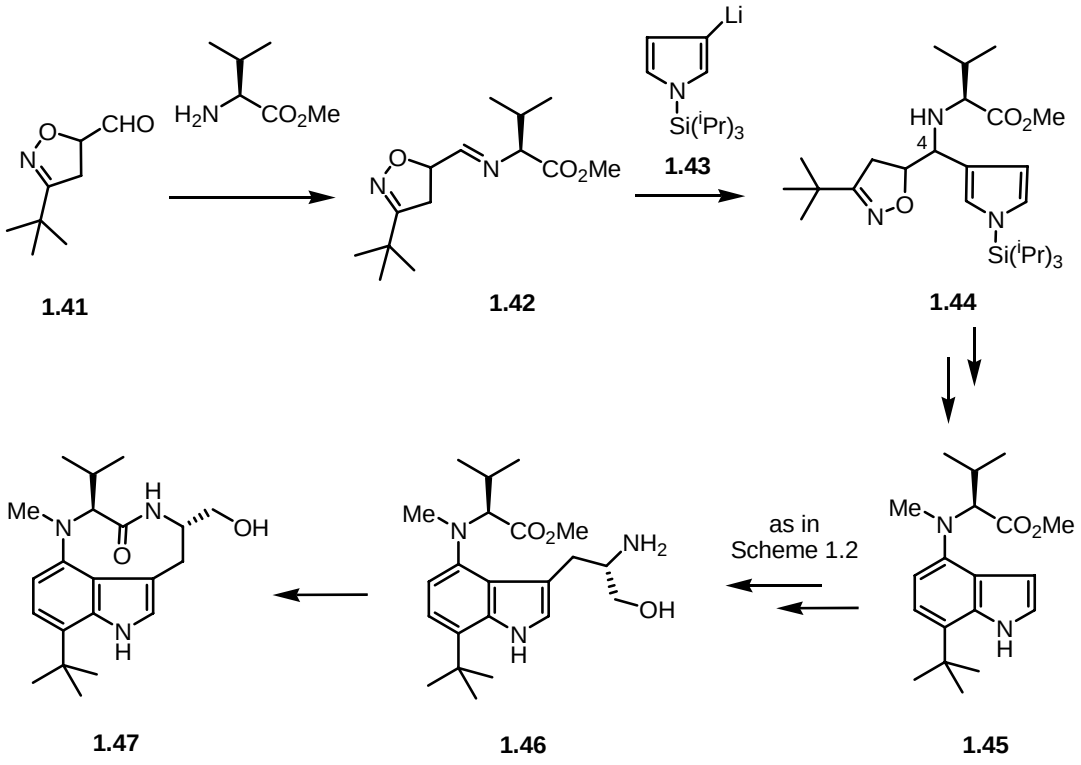



**Scheme 1.3** Highlights of Semmelhack and Rhee formal total synthesis of lyngbytoxin A (**1.1**).

Besides the total syntheses of the teleocidins several groups have reported interesting approaches towards simplified analogues.

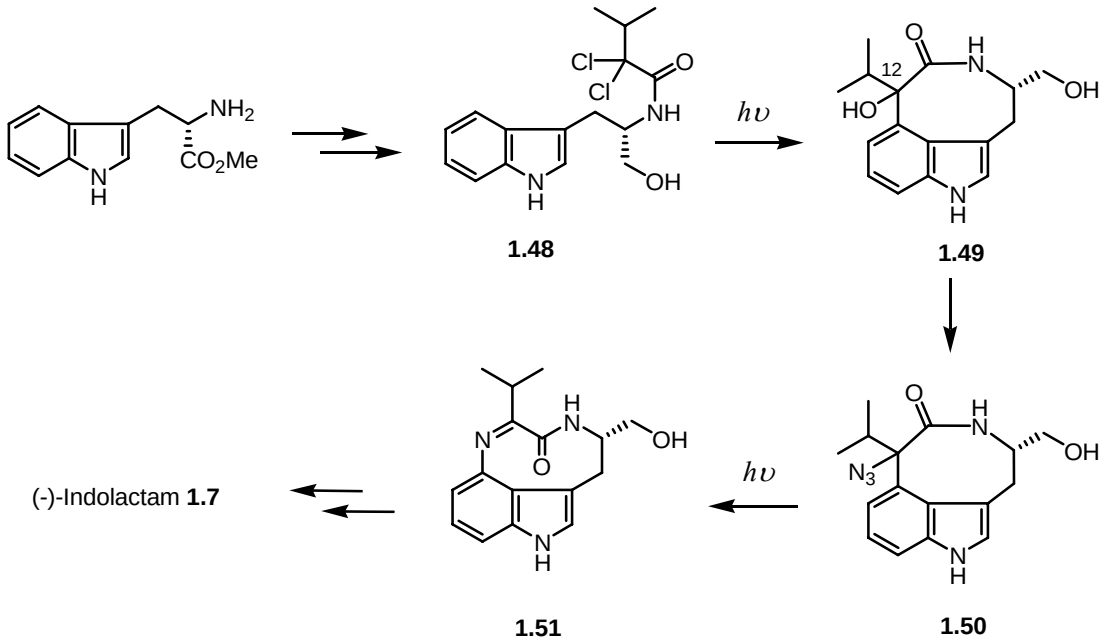
The Kozikowski approach[1.37] to this type of compounds is similar to that of Natsume in that the indolic system is constructed from a functionalized pyrrole. The synthesis of teleocidins A analogue (**1.47**) involved the condensation of *N*-(triisopropylsilyl)-*β*-lithiopyrrole (**1.43**) with the imine (**1.42**), which was obtained from the reaction of L-valine methyl ester with the isoxaline (**1.41**), affording pyrrole (**1.44**) as mixture of diastereomeric products at C-4. The indole nucleus is obtained *via* the hydrogenolysis of the N-O bond followed by cyclization using TBDMSOTf. Functionalization of the indole 3-position of (**1.45**) was achieved in the same manner as in Scheme 1.2. The formation of the nine-membered lactam ring was efficiently accomplished with $Et_3Al$ (Scheme 1.4).

[1.37] Kozikowski, A. P.; Sato, K.; Basu, A.; Lazo, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 6228.




**Scheme 1.4** Highlights of Kozikowski's synthesis of teleocidins analogue (**1.47**).

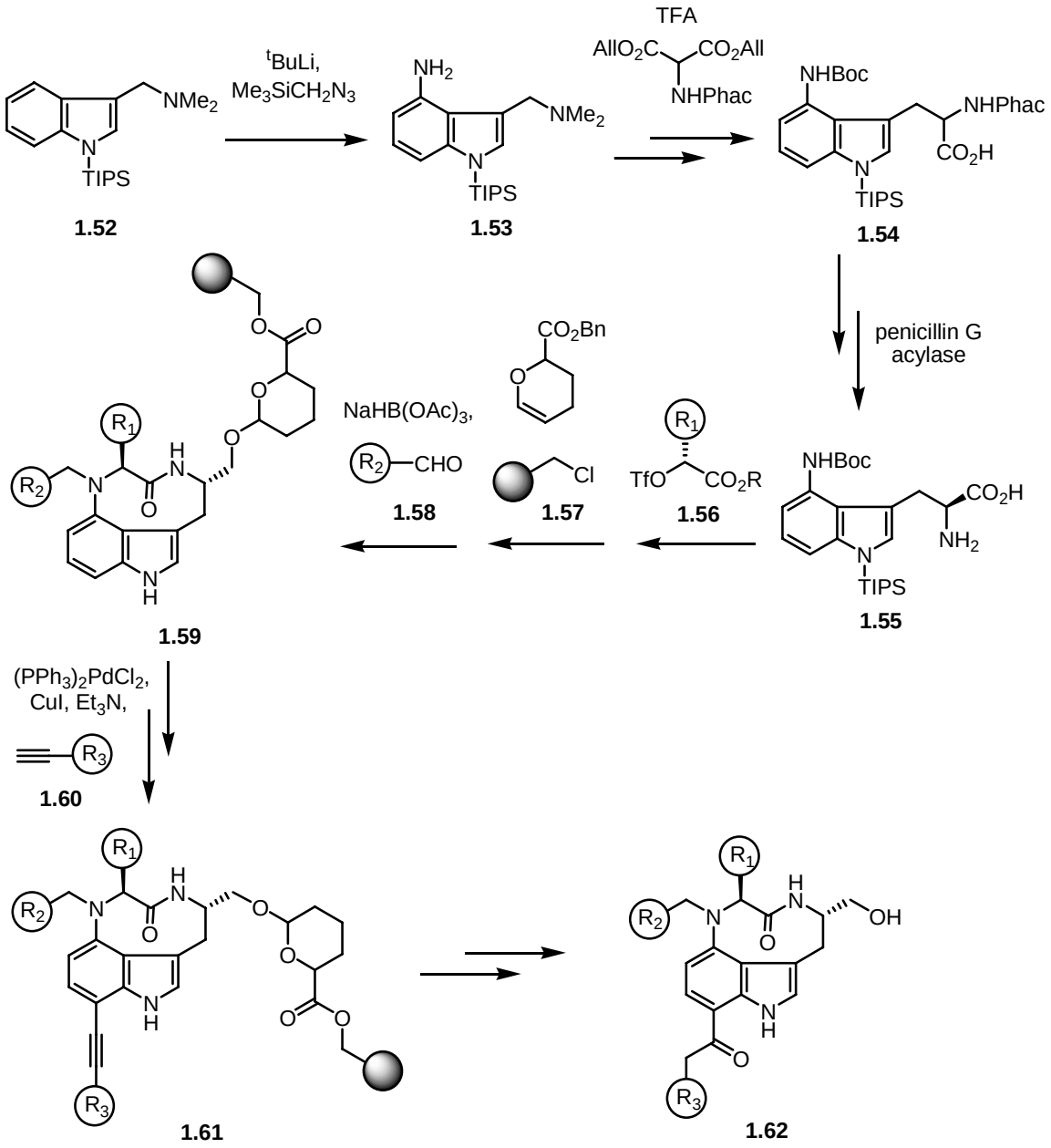
In most of the approaches towards the indolactam core, the 9-membered lactam ring is obtained by formation of the amide bond, thus requiring functionality in both the 3- and 4-positions of the indole nucleus (*e.g.*, as in Scheme 1.2 to Scheme 1.4). Moody and Mascal[1.33c] prepared (-)-ILV (**1.7**) by a fundamentally different approach, in that only the indole 4-position is previously functionalized. The key step involves the photocyclization of trytophanol (**1.48**), easily obtained from (-)-tryptophan methyl ester, to afford the tertiary alcohol (**1.49**) as an epimeric mixture at C-12. Conversion into the corresponding azide (**1.50**) followed by a nitrene-mediated ring expansion afforded imine (**1.51**). A stereoselective reduction followed by *N*-methylation then delivered (-)-ILV (Scheme 1.5).




**Scheme 1.5** Highlights of Moody and Mascal total synthesis of (–)-ILV (**1.7**).

Waldmann and co-workers constructed a library of teleocidin A analogues.[1.38] Regioselective lithiation of dimethyl *N*-gramine derivative (**1.52**) followed by treatment with TMS-diazomethane afforded 4-amino indole (**1.53**) which was then converted into the corresponding substituted tryptophan (**1.54**) by treatment with TFA and diallyl phenylacetamidomalonate. Enantioselective enzymatic hydrolysis afforded enantiomerically pure amino-acid (**1.55**). The second stereocenter in the indolactam core was introduced by alkylation with different homochiral $\alpha$-hydroxy acid ester triflates (**1.56**) and the primary hydroxyl group was used to link the indolactam core to solid phase *via* a tetrahydropyrane spacer. Reductive amination with different aldehydes (**1.58**) was achieved with $NaHB(OAc)_3$ yielding resin-linked indolic tertiary amines derivatives (**1.59**). The C-7 position of the indole nucleus was then functionalized in a sequence that involved as the key step the Sonogashira coupling with acetylenes (**1.60**) affording immobilized alkynes (**1.61**) which were successfully released from the polymeric support as the corresponding ketones (**1.62**).

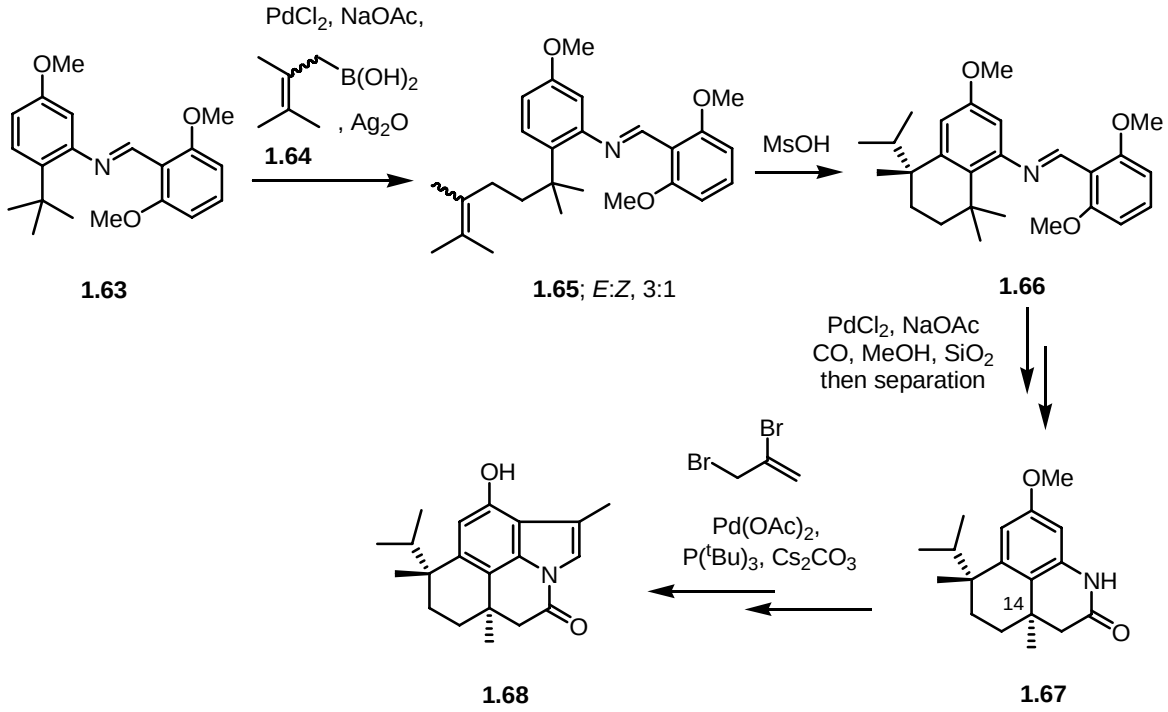
[1.38] (a) Meseguer, B.; Alonso-Díaz, D.; Griebenow, N.; Herget, T.; Waldmann, H. *Angew. Chem. Int. Ed.* **1999**, *38*, 2902. (b) Meseguer, B.; Alonso-Díaz, D.; Griebenow, N.; Herget, T.; Waldmann, H. *Chem. Eur. J.* **2000**, *21*, 2902.




**Scheme 1.6** Highlights of solid phase synthesis of teleocidin A analogues by Waldmann and co-workers.

The teleocidins B core was recently accessed by Sames and co-workers in an impressive sequence involving two carbon-carbon bond formation reactions *via* C-H activation reactions. Treatment of the Schiff base (**1.63**) with stoichiometric amounts of $PdCl_2$ and NaOAc, followed by transmetalation with vinyl boronic acid (**1.64**) afforded alkene (**1.65**) as a 3:1 *E*:*Z* mixture. The latter was then converted into racemic imine (**1.66**) *via* a Friedel-Crafts reaction. A diastereoselective one-carbon

homologation of (**1.66**) was achieved by treating it with $PdCl_2$ and NaOAc followed by addition of CO and MeOH. Acid hydrolysis of the Schiff base accompanied by spontaneous cyclization furnished lactam (**1.67**). The highest selectivity in favour of the desired lactam (**1.67**) was obtained by performing this sequence at 70 °C: with these conditions a 6:1 diastereomeric ratio at C-14 was obtained. The latter was obtained diastereomeric pure by crystallization. The synthesis of the teleocidin B-4 core (**1.68**) was then accomplished *via* the allylation of (**1.67**) with 2,3-dibromopropene followed by a Pd-catalyzed intramolecular alkenylation.

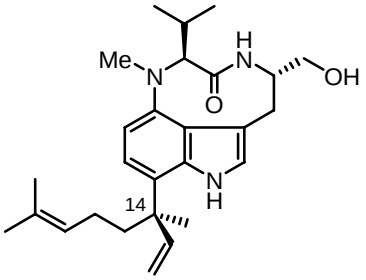



**Scheme 1.7** Highlights of Sames and co-workers synthesis of teleocidin B-4 core.

# CHAPTER 2
# Synthetic Strategy Towards Lyngbyatoxin A

## 2.1 - Installation of the Quaternary Centre

Although the field of stereoselective synthesis has witnessed spectacular progress in the past decades, the enantioselective formation of all-carbon quaternary centres still poses a considerable challenge to the synthetic organic chemist.[2.1] Regarding the teleocidin alkaloids, all of the thus far reported total syntheses lack stereochemical control at the quaternary centre(s) (*vide* Chapter 1).




**1.1**

**Figure 2.1** Structure of lyngbyatoxin A.

Therefore, a critical step in any enantioselective approach to lyngbyatoxin A concerns the installation of the quaternary stereocenter at C-14.

A possible solution to the stereocontrolled generation of the characteristic all-carbon quaternary centre present in the teleocidins A involves the use of the so-called Jung rearrangement.[2.2] The Jung rearrangement refers to the Lewis acid (LA) mediated stereospecific rearrangement of enantiomerically pure epoxides (**2.1**) into the corresponding carbonyl compound (**2.5**) and thus it has the potential to establish an acyclic quaternary carbon (marked * in (**2.5**)) (Scheme 1.1).[2.3]

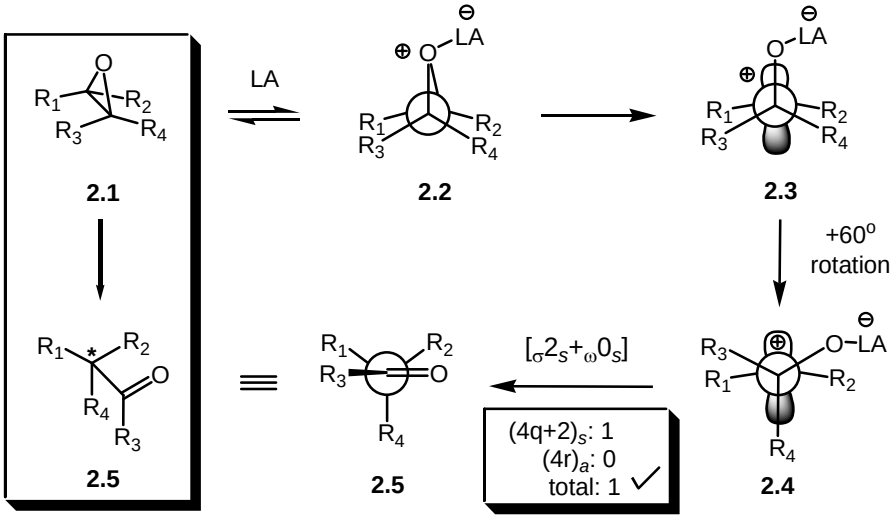
---

[2.1] For reviews on the synthesis of quaternary carbon centers see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591. (c) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Christoffers, J.; Baro, A. in "Quaternary Stereocenters, Challenges and Solutions for Organic Synthesis" **2005**, Wiley-VCH, New York. (d) Barriault, L.; Denissova, I. *Tetrahedron* **2003**, *42*, 1688.

[2.2] (a) Jung, M. E.; D´Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379. (b) Jung, M. E.; Anderson, K. L. *Tetrahedron Lett.* **1997**, *38*, 2605.

[2.3] For a review on the acid catalysed rearrangements of epoxides see: Rickborn, B. in "Comprehensive Organic Synthesis*"* (Trost, B. M., Fleming, I. ed.) **1991**, *3*, 733, Pergamon, New York.

Mechanistically, the Jung rearrangement is reminiscent of the better known pinacol rearrangement.[2.4] It is a step-wise process that starts with the formation of the epoxide-L.A. complex (**2.2**), which undergoes rupture of the oxirane C-O bond to afford (the most) stabilized carbocation (**2.3**). Rotation around the carbon-carbon bond into conformer (**2.4**), a process required to align the migrating group with the adjacent vacant p orbital in a coplanar fashion, followed by a symmetry-allowed 1,2-sigmatropic shift[2.5] finally produces carbonyl compound (**2.5**).[2.2a]




**Scheme 1.1** The Jung rearrangement.

It should however be appreciated that the outcome of this sequence, being determined by a subtle combination of intrinsic factors (*e.g.*, carbocation stability and migratory aptitude of the substituents) and reaction conditions, is often difficult to predict and control.[2.6] This point is adequately illustrated in the initial studies by Tanner and Tønder towards the enantioselective total synthesis of lyngbyatoxin A where it was found that the result of the Jung rearrangement of enantiomerically pure indole-

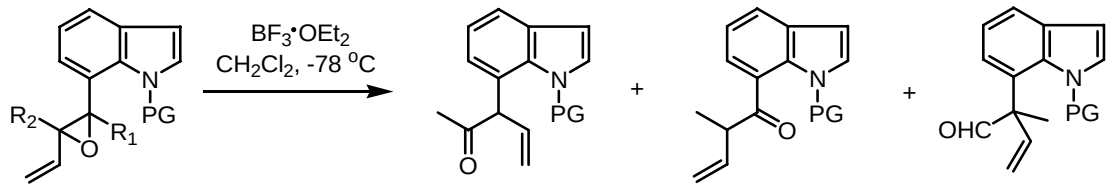
[2.4] (a) Mayo, P. in "Rearrangement in Ground and Excited States*"* **1980**, *1*, Academic Press, New York). (b) Isaacs, N. S. in "Reactive Intermediates in Organic Chemistry" **1974**, Wiley, New York. (c) Coveney, D, J. in "Comprehensive. Organic Synthesis" (Trost, B. M.; Fleming, I. ed.) **1991**, *3*, 777, Pergamon, New York. (d) Rickborn, B. in "Comprehensive Organic Synthesis" (Trost, B. M.; Fleming, I. ed.) **1991**, *3*, 721, Pergamon, New York.

[2.5] (a) Woodward, R. B.; Hoffmann, R. in "The Conservation of Orbital Symmetry" **1970**, Verlag Chemie, Academic Press, New York. (b) Fleming, I. in "Pericyclic Reactions", **1999**, *67*, Oxford Science Publications, Oxford Chemistry Primers.

[2.6] See *e.g.*, Collins, C. J. *Acc. Chem. Res.* **1971**, *4*, 315 and examples therein.

derived vinyl epoxides (**2.6**) is highly dependent of the nature of the indole protective group (PG) and of the substitution pattern of the oxirane ring.[2.7]

**Table 2.1** Product distribution in the Jung rearrangement of indole-derived vinyl epoxides (**2.6**).




**2.6** **2.7** **2.8** **2.9**

| Substrate | Product Distribution | | |
|---|---|---|---|
| | **2.7** | **2.8** | **2.9** |
| **2.6a**: PG = Bn, $R_1$ = H, $R_2$ = Me | >99% (*via* vinyl migration) | - | - |
| **2.6b**: PG = Ts, $R_1$ = H, $R_2$ = Me | - | 60% (*via* hydride migration) | 40% (*via* indole migration) |
| **2.6c**: PG = Bn, $R_1$ = Me, $R_2$ = H | - | - | >99% (*via* vinyl migration) |

Therefore, hoping to avoid the rearrangement capriciousness, it was decided to incorporate it at an early stage in the synthetic sequence, namely *prior* to formation of the indole moiety. In this approach, the substrate for the Jung rearrangement would then be an enantiomerically pure, conveniently functionalized vinyl phenyl epoxide (**2.10**) or (**2.11**)[2.8] and the indole nucleus would be accessed at a later stage *via* some type of annulation strategy (*vide infra*, section 2.2).

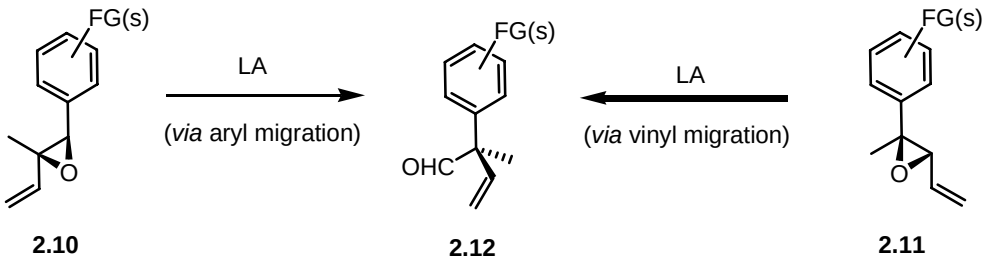
Furthermore, in order to circumvent the issue concerning the migratory aptitude of functionalized phenyl moieties,[2.9] it was decided to investigate the feasibility of

[2.7] Tønder, J. E.; Tanner, D. *Tetrahedron* **2003**, *59*, 6937.

[2.8] Jung and Anderson already demonstrated that benzylic quaternary carbon centres could be obtained in high yield and with excellent optical purity from enantiomerically pure (non-substituted) phenyl vinyl epoxides *via* phenyl migration. See ref. 2.2b.

[2.9] For studies on the relative migratory aptitudes of substituted aryl groups in the pinacol rearrangement see: (a) Bachmann, W. E.; Ferguson, J. W. *J. Am. Chem. Soc.* **1934**, *56*, 2081; (b) Curtin, D. Y.; Crew, M. C. *J. Am. Chem. Soc.* **1955**, *77*, 354.

accessing the quaternary carbon *via* vinyl migration,[2.10] as opposed to the alternative aryl migration (Scheme 2.2).



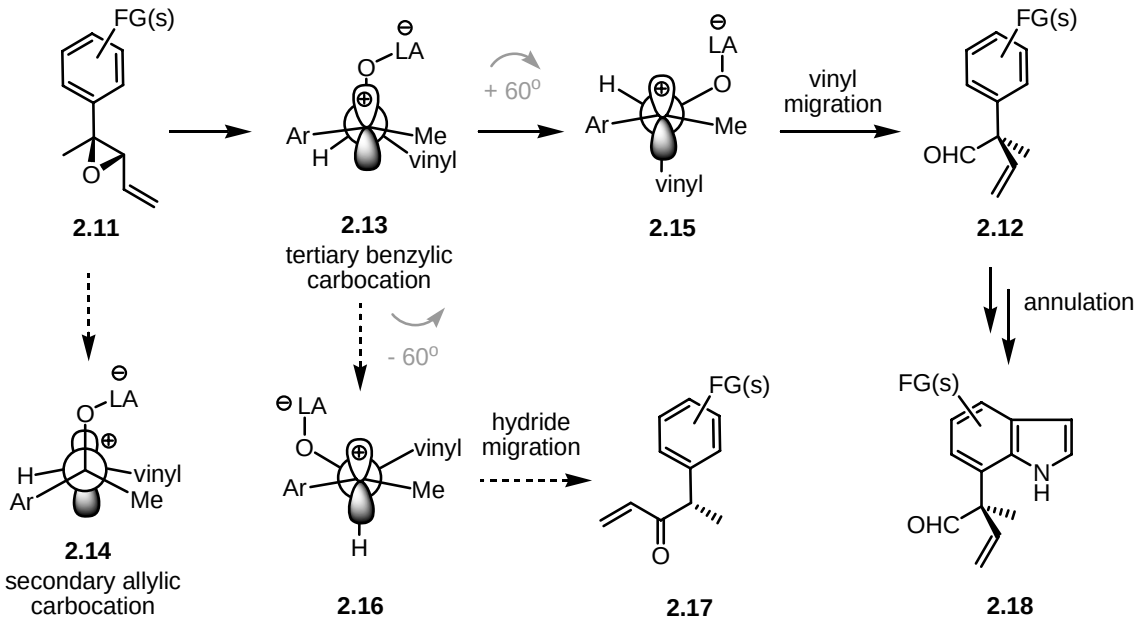

**2.10** **2.12** **2.11**

**Scheme 2.2** Two possibilities for accessing the all-carbon quaternary centre *via* the Jung rearrangement.

That the quaternary aldehyde (**2.12**) would be the exclusive/major product from the Jung rearrangement of (**2.11**) was expected on several grounds. Firstly, the anticipated preference for the tertiary benzylic carbocation (**2.13**) over the secondary allylic (**2.14**) finds good precedent in the work of Jung who already showed that a secondary benzylic carbonium ion is more stable than its secondary allylic counterpart.[2.2b] Secondly, the clock-wise rotation that correctly aligns the vinyl group for migration (conformer (**2.15**)), thus leading to quaternary aldehyde (**2.12**), is also expected to be favoured over the alternative counter clock-wise motion (Scheme 2.3). This is because such clock-wise rotation requires the hydrogen, the least steric demanding species, to eclipse with the aryl group. The opposite anti clock-wise process, that collinearly aligns the hydrogen with the adjacent p orbital (conformer (**2.16**)) and leads to *α*,*β*-unsaturated ketone (**2.17**) *via* a 1,2-hydride shift, would require the vinyl group to cross with the methyl group, thereby causing what is expected to be a more severe eclipsing interaction. Finally, migration of the vinyl group is also expected to be favoured over the hydride on the grounds of its (slightly) higher migratory aptitude.[2.11]

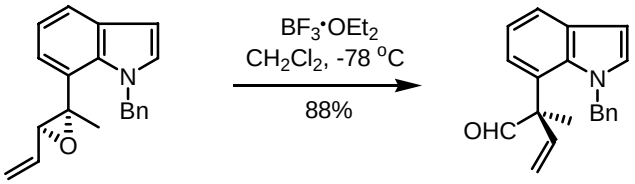
[2.10] Jung and Anderson have previously reported that 1,2-vinyl shifts in these type of systems proceed with good chirality transfer. See refs. 2.2.

[2.11] Nakamura, K.; Osamura, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9112 and references therein.




**Scheme 2.3** Possible pathways during the Jung rearrangement of vinyl epoxide (**2.11**).

In the context of asymmetric synthesis, besides the regiochemical aspects of the Jung rearrangement discussed above, an equally important feature concerns the rearrangement stereospecificity. Ideally, the enantiomeric purity of the starting epoxide will be reflected in that of the product. However, this is not always the case: Tanner and Tønder disclosed that their initial approach to the installation of the quaternary carbon in lyngbyatoxin A was plagued by a substantial loss of enantiomeric purity during the Jung rearrangement of vinyl epoxide (**2.6c**) (91% *ee*) to the quaternary aldehyde (**2.9**) (71% *ee*) (Scheme 2.4).[2.7]

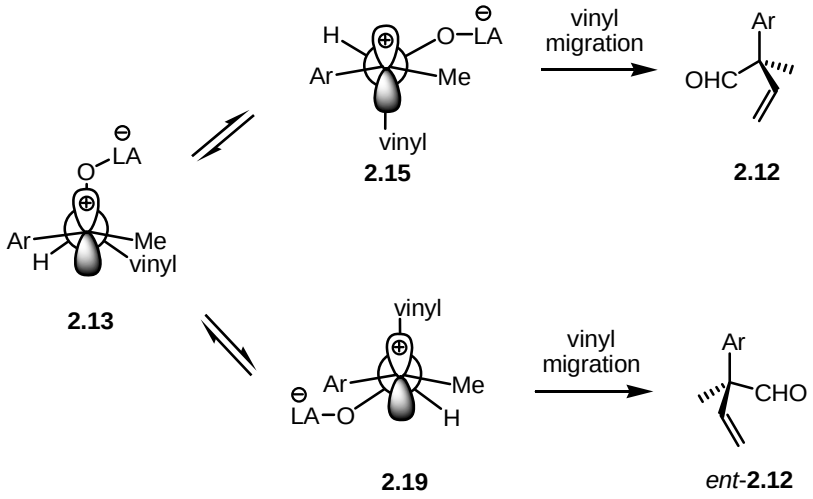



**(*S*,*S*)-2.6c**, 91% *ee* **(*R*)-2.9**, 71% *ee*

**Scheme 2.4** Non-stereospecific Jung rearrangement of epoxide (**2.6c**) to aldehyde (**2.9**).

In order to achieve complete chirality transfer from epoxide (**2.11**), the rate of vinyl migration has to be significantly higher than the rate of conformer equilibration. If not, conformer (**2.19**) will also be appreciably populated and thus vinyl migration onto the enantiotopic face of the planar carbocation becomes a significant competing

process. This would lead to enantiomeric quaternary aldehyde *ent*-**(2.12**) and therefore to a decrease in the optical purity (Scheme 2.5). Encouragingly, Jung and Anderson already reported that 1,2-vinyl shifts in (simple) phenyl-derived vinyl epoxides can proceed with good transfer of the chirality.[2.2]




**Scheme 2.5** Conformer equilibration leading to a stereochemical loss during the Jung rearrangement.

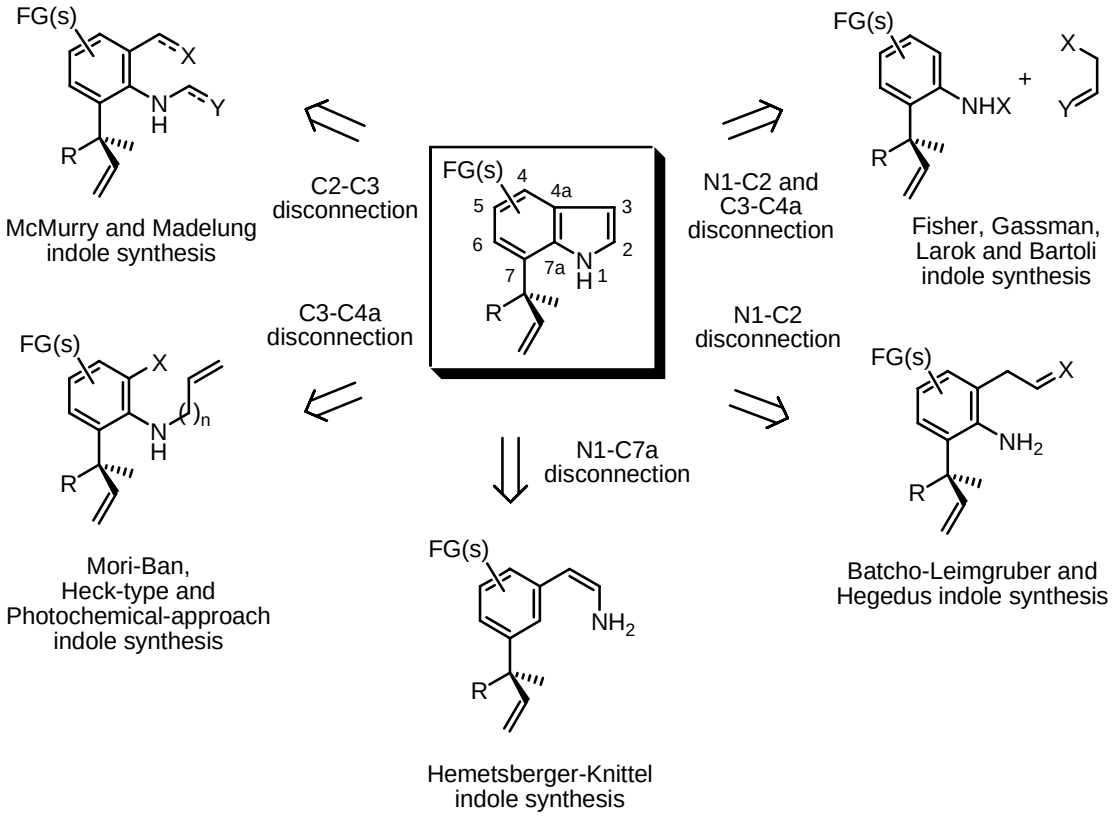
## 2.2 - Construction of the Indole Ring

Having defined a strategy to install the quaternary centre in lyngbyatoxin A, we turned our attention to the synthesis of the indole ring system.

A variety of methods for preparing indoles from non-heterocyclic precursors by cyclization of suitably substituted benzenes is available (Scheme 2.6).[2.12] As it can be seen, most of these annulation-based approaches require highly functionalized benzene-derived substrates, the synthesis of which presents a challenge on itself. Furthermore, the majority of these methods entails the pre-functionalization of the aromatic position *ortho* to the quaternary carbon, typically with a protected amino group or a synthetic equivalent. However, any such *ortho* functionality can conceivably interfere with the preparation of the rearrangement substrates (*e.g.*, the

[2.12] For leading references see: (a) Sundberg, R. J. in "Indoles" **1996**, Academic Press, San Diego. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans 1* **2000**, 1045. (c) Gribble, G. W. *Contemp. Org. Synth.* **1994**, 145. (d) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2848. (e) Moody, C. J. *Synlett* **1994**, 681.

fixed proximity between the nucleophilic (protected) amino group and the electrophilic oxirane ring presumably makes such benzylic epoxides rather labile) and/or the course of the Jung rearrangement itself. Therefore, these approaches were *a priori* considered to be highly risky.



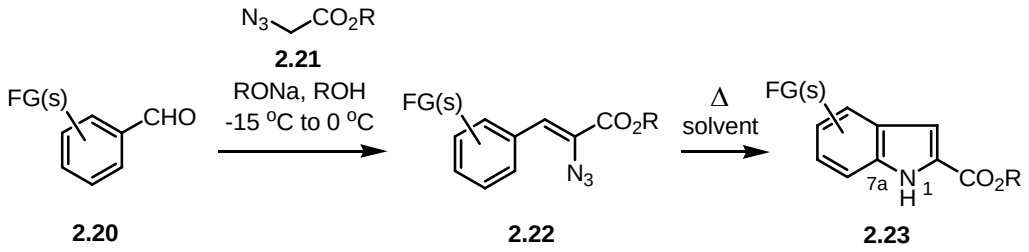

**Scheme 2.6** Example of indole synthesis *via* cyclization of substituted benzenes.

On the other hand, the Hemetsberger-Knittel indole synthesis[2.13,2.14] emerged as being particularly suitable to our needs. The Hemetsberger-Knittel approach involves the formation of 2-azidocinnamates (**2.22**) by condensation of a benzaldehyde (**2.20**) with an azidoacetate (**2.21**) in the presence of sodium alkoxide at low temperatures as the first step and pyrolysis of (**2.22**) in a convenient solvent as the second step to give the

[2.13] (a) Hemetsberger, H.; Knittel, D.; Weidmann, H. *Monatsh. Chem.* **1969**, *100*, 1599-1603. (b) Hemetsberger, H.; Knittel, D.; Weidmann, H. *Monatsh. Chem.* **1970**, *101*, 161-165. (c) Hemetsberger, H.; Knittel, D. *Monatsh. Chem.* **1972**, *103*, 194-204. (d) Murakami, Y.; Watanabe, T.; Suzuki, H.; Kotake, N.; Takahashi, T.; Toyonari, K.; Ohno, M.; Takase, K.; Suzuki, T.; Kondo, K. *Chem. Pharm. Bull.* **1997**, *45*, 1739.

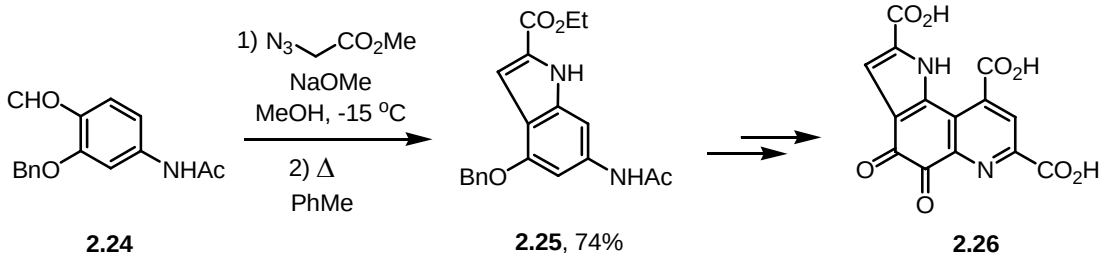
[2.14] For a general review dealing with nitrenes see: Moody, C. J. in "Comprehensive. Organic Synthesis." (Trost, B. M.; Fleming, I. ed.) **1991**, *1*, 21, Pergamon, New York.

corresponding indole-2-carboxylate (**2.23**). Thus, this approach to indoles has the advantage of requiring less substituted benzene derivatives as starting materials and, since the indole-forming process can be seen as a formal nitrene insertion into the aromatic C-H bond corresponding to formation of the N1-C7a bond, it does not require pre-functionalization of the aromatic positions *ortho* to the quaternary carbon. Furthermore, the reaction is compatible with various functional groups (FGs) (*e.g.*, halogens, ethers, amides, etc).




**Scheme 2.7** The Hemetsberger-Knittel indole synthesis.

These features are nicely illustrated in the synthesis of indole (**2.25**), an advanced intermediate in the total synthesis of the bacterial coenzyme methoxatin (**2.26**), which was prepared from the highly functionalized benzaldehyde (**2.24**) in good yield (74%) (Scheme 2.8).

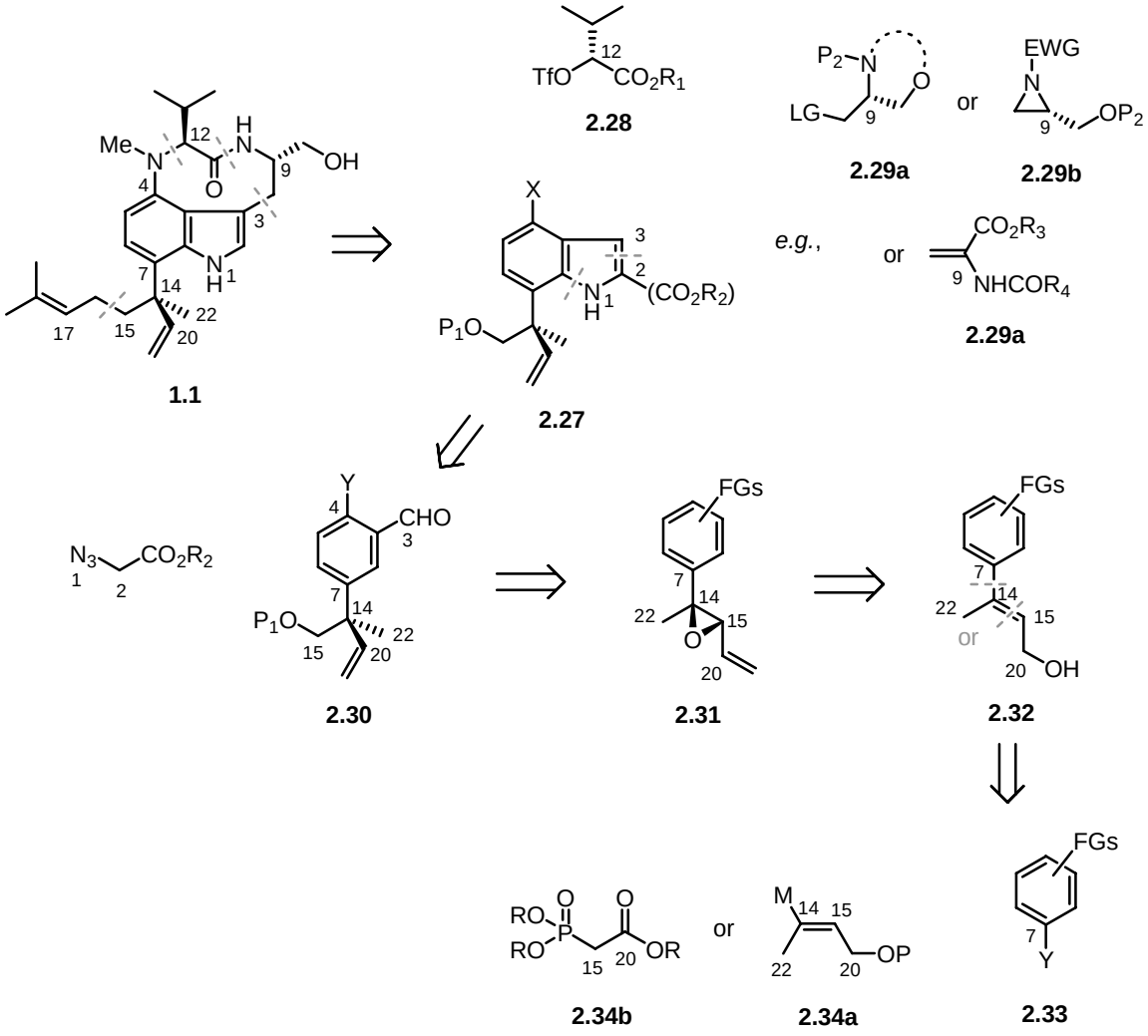



**Scheme 2.8** Use of the Hemetsberger-Knittel reaction as the key step in the total synthesis of methoxatin (**2.26**).

On the down-side, although the Hemetsberger-Knittel indole synthesis is simple and convenient, it is limited to aryl aldehydes and thus 3-substituted indoles are usually not available through this method. The overall reaction yields are typically good; when this is not the case, the reason for the low yields of indoles lies mainly in the first step, the preparation of azidocinnamates (**2.22**).[2.13d]

## 2.3 - Retrosynthetic Analysis of Lyngbyatoxin A

The retrosynthetic guidelines for lyngbyatoxin A based on the key steps discussed above, *i.e.*, installation of the quaternary carbon centre *via* the Jung rearrangement and construction of the indole nucleus by a Hemetsberger-Knittel cyclization, are shown in Scheme 2.9.




**Scheme 2.9** Retrosynthetic guidelines for lyngbyatoxin A.

Retrosynthetically, the 9-membered lactam ring in lyngbyatoxin A (**1.1**) would be accessed at a late stage by a macrolactonization protocol,[2.15] while the L-valine unit would be introduced *via* a $S_N2$ reaction of aminoindole (**2.27**, X = NHMe) with chiral triflate (**2.28**).[2.15d] Importantly, delaying to a very late stage in the synthesis the construction of the 9-membered lactam, which is critical for the biological activity of lyngbyatoxin A, should reduce the risk of handling potential tumor promoting compounds.

Several possibilities are available for the introduction of the amino-alcohol moiety at the (intrinsically nucleophilic) 3-position of the indole nucleus.[2.16] Enantiomerically pure substituted tryptophanols have been prepared from indoles by reaction with chiral oxazolidinone-derivatives (**2.29a**)[2.16a,b] and chiral azidirines (**2.29b**).[2.16c-g] Alternatively, a Heck-coupling with acetamidoacrylate (**2.29c**) followed by asymmetric reduction has also been reported.[2.16h-k] Other possibilities include the use of Schöllkopf chiral auxiliary[2.16l,m] and enzymatic resolution (not shown).[2.16n,o]

At a suitable stage, the linalyl side chain would be constructed *via* a Wittig-type homologation followed by a $S_N2$ displacement with a 2-methylpropene organometallic reagent (not shown).

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[2.15] For some examples see: (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1987**, *28*, 2265. (b) Muratake, H.; Natsume, M. *Tetrahedron.* **1991**, *47*, 8535. (c) Muratake, H., Natsume, M. *Tetrahedron* **1991**, *47*, 8545. (d) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1399.

[2.16] For leading references see: i) **chiral oxazolidinone** (a) Pyun, D. K.; Lee, C. H.; Ha, H.-J.; Park, C. S.; Chang, J.-W.; Lee, W. K. *Org. Lett.* **2001**, *3*, 4197. (b) Sibi, M. P.; Rutherford, D.; sharma, R. *J. Chem. Soc. Perkin Trans. I* **1994**, 1675. ii) **chiral aziridines** (c) Ezquerra, J.; Pedragal, C.; Lamas, C.; Pastor, A.; Alvarez, P.; Vaquero, J. J. *Tetrahedron Lett.* **1996**, *37*, 683. (d) Ezquerra, J.; Pedragal, C.; Lamas, C.; Pastor, A.; Alvarez, P.; Vaquero, J. J. *Tetrahedron* **1997**, *53*, 8237. (e) Nenajdenko, V. G.; karpov, A. S.; Balenkova, E. S. *Tetrahedron: Asymmetry* **2001**, *12*, 2517. (f) Nishikawa, T.; Ishikawa, M.; Isobe, M. *Synlett* **2001**, 945. (g) Yadav, J. S.; Reddy, B. V. S.; Abraham, S.; Sabitha, G. *Tetrahedron Lett.* **2002**, *43*, 1565. iii) **Heck and asymmetric hydrogenation** (h) Osanai, K.; Yokayama, Y.; Kondo, K.; Murakami, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1587. (i) Wang, W.; Cai, M.; Xiong, C.; Zhang, J.; Trivedi, D.; Hruby, J. V. *Tetrahedron* **2002**, *58*, 7365. (j) Wang, W.; Xiong, C.; Yang, J. Hruby, J. V. *Tetrahedron Lett.* **2001**, 7717. (k) Yokayama, Y.; Matsumoto, T.; Murakami, Y. *J. Org. Chem.* **1995**, *60*, 1486. iv) **Schöllkopf chiral auxiliary** (l) Ma, C.; Yu, S. Y.; He, X.; Liu, X.; Cook, M. J. *Tetrahedron Lett.* **2000**, *41*, 2781. (m) Zhang, P.; Liu, R.; Cook, J. M. *Tetrahedron Lett.* **1995**, *36*, 7411. v**) enzymatic resolution** (n) Konda-Yamada, Y.; Okada, C. Yoshida, K.; Umeda, Y.; Arima, S.; Sato, N.; Kai, T.; Takayanagi, H.; Harigaya, Y. *Tetrahedron* **2002**, *58*, 7851. (o) Yokayama, Y.; hara, R.; Kato, N.; Murakami, Y.; Okuno, H. *Heterocycles* **2005**, *6*5, 1455.

Depending on the initial functionalities present on the phenyl ring, it may be necessary to introduce the C-4 amino group. If so, this is planned to be accomplished at a convenient stage *via* a Buchwald-Hartwig coupling,[2.17] a Curtius-type rearrangement[2.18] or electrophilic amination.[2.19]

The indole nucleus is planned to be assembled *via* the Hemetsberger-Knittel reaction of the azidocinnamate obtained by condensation of arylaldehyde (**2.30**) with azidoacetate.[2.13]

The all carbon quaternary stereocenter was intended to be accessed *via* the enantiospecific Jung rearrangement[2.2] of chiral vinyl epoxide (**2.31**), which in turn could be obtained from allylic alcohols (**2.32**) by means of the Sharpless asymmetric epoxidation reaction.[2.20] The later could be obtained from the conveniently functionalized benzene derivative (**2.33**) *via* a coupling reaction[2.21] with alkene (**2.34a**) or a Horner-Wadsworth-Emmons (HWE) reaction[2.22] with phosponate (**2.34b**).

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[2.17] For selected references see: (a) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Frost, C. G.; Mendonça, P. *J. Chem. Soc., Perkin Trans. I* **1998**, 2615. (d) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (e) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (f) Lee, S.; Jørgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729.

[2.18] (a) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023. (b) Smith, P. A. S. *Org. React.* **1946**, 337. (c) Chen, J. J.; Hinkely, J. M.; Wise, D. S.; Townsend, L. B. *Synth. Commun.* **1996**, *26*, 617. (d) Migawa, M. T; Swayze, E. E. *Org. Lett.* **2000**, *2*, 3309.

[2.19] (a) Genet, J. P.; Greck, C. *Synlett* **1997**, 741-749. (b) Zheng, N.; Armstrong III, J. D.; McWilliams, J. C.; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 2817-2820. (c) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947-1980.

[2.20] (a) Gao, Y.; Hanson, M.; Klunder, J. M.; Ko, S. Y.; Masumane, Sharpless, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 5765. For a comprehensive review see (b) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

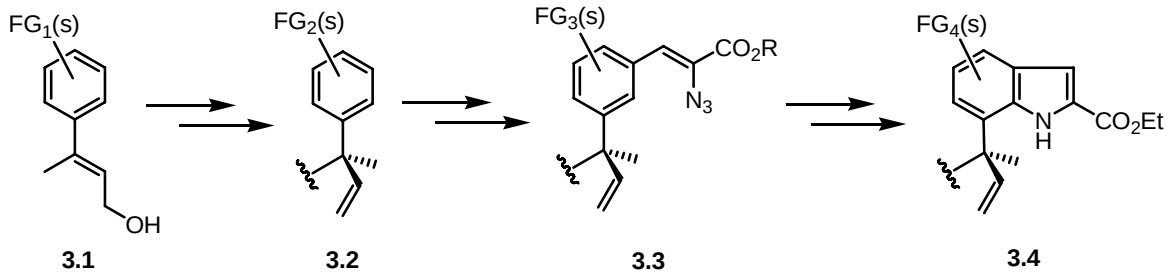
[2.21] For a general reference of coupling reactions see: "Metal-Catalyzed Cross-Coupling Reactions" (De Meijere, A.; Diederich, F. ed.) **2004**, *1&2*, Wiley-VHC, New York.

[2.22] (a) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. (b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *62*, 1733. For a review see (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1988**, *89*, 863.

# CHAPTER 3
# Synthetic Studies Towards Lyngbyatoxin A
# Results and Discussion

## 3.1 - Installation of the All-Carbon Quaternary Stereocenter

The implementation of the synthetic strategy previously discussed for lyngbyatoxin A (*vide* Chapter 2) implies firstly the identification of the functional groups (FGs) in the phenyl moiety that will allow the enantioselective installation of the all-carbon quaternary stereocenter by means of the Jung rearrangement[3.1] (*i.e.*, from (**3.1**) to (**3.2**)) and, at a later stage, permit the construction of the indole nucleus *via* the Hemetsberger-Knittel reaction[3.2] (*i.e.*, from (**3.2**) to (**3.4**)) (Scheme 3.1).




**Scheme 3.1**

### 3.1.1 - Preparation of the Relevant Allylic Alcohols

With this in mind, several allylic alcohols (**3.1**) with relevant phenyl substitution patterns were chosen. From a convergency point of view, it would be advantageous to have an amino group, embryonic to the *N*-methyl amino moiety at C-4 in lyngbyatoxin A, installed from the very beginning (as in allylic alcohols (**3.5**) and (**3.6**)). Alternatively, this amino functionality could be accessed by means of a Curtius

[3.1] (a) Jung, M. E.; D´Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379. (b) Jung, M. E.; Anderson, K. L. *Tetrahedron Lett.* **1997**, *38*, 2605.

[3.2] (a) Hemetsberger, H.; Knittel, D.; Weidmann, H. *Monatsh. Chem.* **1969**, *100*, 1599-1603. (b) Hemetsberger, H.; Knittel, D.; Weidmann, H. *Monatsh. Chem.* **1970**, *101*, 161-165. (c) Hemetsberger, H.; Knittel, D. *Monatsh. Chem.* **1972**, *103*, 194-204. (d) Murakami, Y.; Watanabe, T.; Suzuki, H.; Kotake, N.; Takahashi, T.; Toyonari, K.; Ohno, M.; Takase, K.; Suzuki, T.; Kondo, K. *Chem. Pharm. Bull.* **1997**, *45*, 1739.

rearrangement[3.3] of a carboxylic acid derivative (as allylic alcohol (**3.7**)) or, *e.g.*, *via* a Buchwald-Hartwig amination[3.4] using a halogenated phenyl substrate (as allylic alcohols (**3.8**) and (**3.9**)) and hence these substitution patterns were also considered (Figure 3.1).

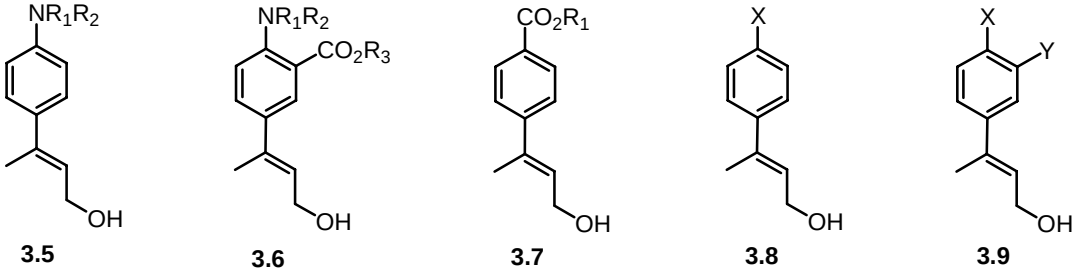



**Figure 3.1** Structure of the allylic alcohols (**3.5**) to (**3.9**) chosen to investigate the implementation of the synthetic strategy towards lyngbyatoxin A.

We therefore started by preparing allylic alcohols of the type shown in Figure 3.1. Focus was put on the expeditious access of such test-compounds rather than on the reaction yields or selectivities.

### 3.1.1.1 - Preparation of Allylic Alcohols Containing a *para*-AminoPhenyl moiety (Types (3.5) and (3.6))

Allylic alcohols with a *para*-amino phenyl moiety, *i.e.*, of the type (**3.5**) and (**3.6**), were initially envisioned to be accessed by means of a stereospecific Stille cross-coupling reaction[3.5] between an enylstannane and a suitable *N*-Boc protected aniline.

---

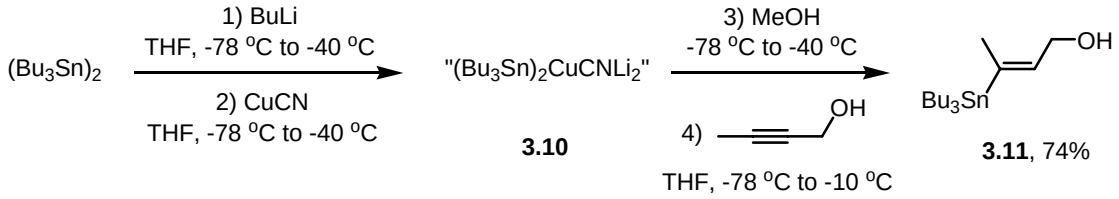
[3.3] (a) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023. (b) Smith, P. A. S. *Org. React.* **1946**, 337. (c) Chen, J. J.; Hinkely, J. M.; Wise, D. S.; Townsend, L. B. *Synth. Commun.* **1996**, *26*, 617. (d) Migawa, M. T; Swayze, E. E. *Org. Lett.* **2000**, *2*, 3309.

[3.4] For selected references see: (a) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Frost, C. G.; Mendonça, P. *J. Chem. Soc., Perkin Trans. I* **1998**, 2615. (d) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (e) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (f) Lee, S.; Jørgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729.

[3.5] (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *101*, 4992. For a comprehensive review see: (d) Farina, V.; Krishnamurphy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. For a review on the intramolecular Stille reaction see: (e) Duncton, M. A. J.; Pattenden, G. J. *Chem. Soc., Perkin Trans. 1* **1999**, 1235.

The choice of the Boc group as the amino protecting group was driven essentially by its efficiency in directed *ortho* metallation (DoM) reactions.[3.6,3.7] This property was anticipated to be important since, in order to access the substrates for the Hemetsberger-Knittel reaction, the introduction of an *ortho* formyl group would be required for allylic alcohols (**3.5**) at a later stage.

The one-pot preparation of enylstannane (**3.11**), previously reported by Pancrazi and co-workers,[3.8] involved the regio- and stereoselective stannylcupration of 2-butyn-1-ol using the "higher order" cyanocuprate (**3.10**), itself obtained from hexabutylditin and CuCN (Scheme 3.2).




**Scheme 3.2** Preparation of enylstannane (**3.11**).

We then attended to the preparation of several potential electrophilic coupling patterns of enylstannane (**3.11**).

*N*-Boc-*para*-Bromoaniline (**3.12a**) was readily obtained in high yield (90%) from *para*-bromoaniline by treatment with $Boc_2O$.[3.9] Similarly, the corresponding triflate (**3.12c**) was prepared from *para*-aminophenol by treatment with $Boc_2O$, followed by reaction with $Tf_2O$ in pyridine (89% over the 2 steps).The corresponding *N*,*N*-diBoc-anilines (**3.13a**) and (**3.13b**) were then obtained, also in high yields (approximately

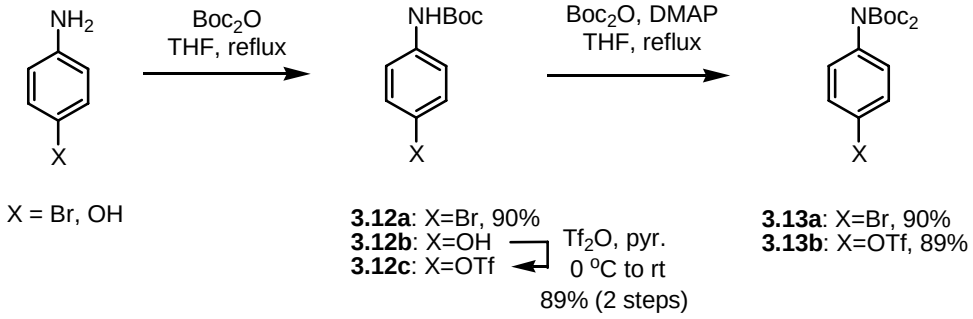
[3.6] For general reviews on DoM see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Narashimahn, N. S.; Mali, R. S. *Synthesis* **1983**, 957.

[3.7] For selected examples where Boc group is used in DoM see: (a) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798. (b) Fishwick, C. W. G.; Storr, R. C.; Manley, P. W. *J. Chem. Soc., Chem. Commun.* **1984**, 1304. (c) Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1984**, *25*, 1304. (d) Reed, J. N.; Rotchford, J.; Strickland, D. *Tetrahedron Lett.* **1988**, *29*, 5725-5728.

[3.8] (a) Betzer, J.-F.; Ardisson, J.; Lallemand, J.-Y.; Pancrazi, A. *Tetrahedron Letts.* **1997**, *38*, 2279. (b) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768. (c) Betzer, J.-F.; Pancrazi, A. *Synlett.*, **1998**, 1129. (d) Betzer, J.-F.; Pancrazi, A. *Synthesis*, **1999**, 629-634. (e) Dominguez, B.; Pazos, Y.; de Lera, A. R. *J. Org. Chem.* **2000**, *65*, 5917.

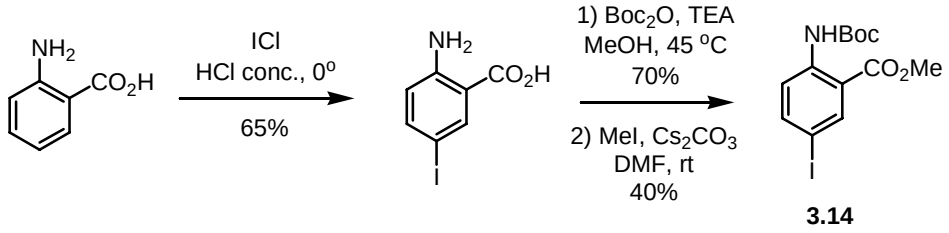
[3.9] Lamothe, M.; Pauwels, P. J.; Belliard, K.; Schambel, P.; Halazy, S. *J. Med. Chem.* **1997**, *40*, 3542. *N*-Boc-*para*-Bromoaniline (**3.12a**) is commercially available from Aldrich.

90%), by exhaustive treatment with $Boc_2O$ in the presence of a catalytic amount of DMAP.[3.10]




**Scheme 3.3** Preparation of aryl bromides (**3.12a**) and (**3.13a**) and aryl triflates (**3.12c**) and (**3.13b**).

The preparation of aryl iodine (**3.14**) was accomplished according to Scheme 3.4. Treatment of antaranilic acid with ICl under acidic conditions delivered *para*-iodo antaranilic acid in good yield (65%).[3.11] Reaction of the later with $Boc_2O$ produced the corresponding *N*-Boc aniline (70%), which was then subjected to nucleophilic estherification with MeI in the presence of $CsCO_3$[3.12] affording iodinated-aniline (**3.14**) in moderate yield (40%).



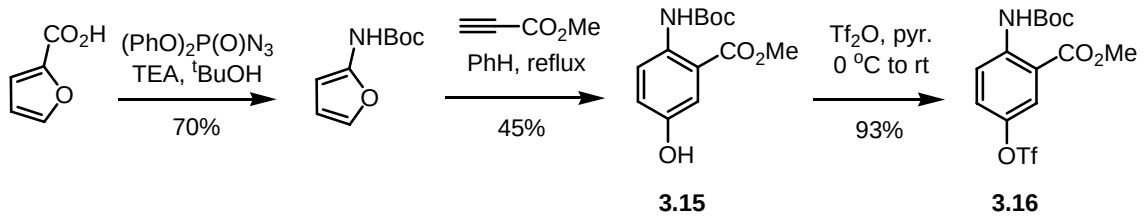

**Scheme 3.4** Preparation of aryl iodide (**3.14**).

[3.10] For a related example see: Grehan, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scandinavica* B **1986**, *40*, 745.

[3.11] Wallingford, V. H.; Krueger, P. A. *Org. Synth. Coll., Vol. II*, 349. *para*-Iodo antaranilic acid is commercially available from Aldrich.

[3.12] For related examples see: (a) Wang, S.-S.; Gisin, B. F.; Winter, D. P.; Makofske, R.; Kulesha, I. D.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 1286. (b) Kruizinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183. (c) Kruizinga, W. H.; Strijtveen B.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4321.

Aryl triflate (**3.16**) was prepared using the methodology developed by Wu and co-workers (Scheme 3.5).[3.13] Treatment of 2-furoic acid with DPPA in $^{t}$BuOH afforded 2-*N*-Boc-aminofurane in good yield (70%), which then participates in a highly regioselective Diels-Alder reaction with methyl propiolate furnishing phenolic carbamate (**3.15**) in moderate yield (45%). Finally, treatment with $Tf_2O$ in pyridine produced aryl triflate (**3.16**) in high yield (93%).




**Scheme 3.5**. Preparation of aryl triflate (**3.16**).

The Stille coupling reaction between enylstannane (**3.11**) and the *N*-Boc anilines (**3.12a**), (**3.12c**), (**3.13a**), (**3.13b**), (**3.14**) and (**3.16**) was then investigated by screening some of the most common conditions[3.5d] used for this reaction (Table 3.1). For *N*-Boc bromoanilines (**3.12a**) and (**3.13a**) and for the *N*-Boc iodoaniline (**3.14**) the use of $Pd(PPh_3)_4$, $Pd_2(dba)_3{\cdot}CHCl_3$ and $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of $AsPh_3$ and CuI was examined. For aryl triflates (**3.12c**), (**3.13b**) and (**3.16**), we tested the use of $Pd(PPh_3)_4$, with and without LiCl, as well as $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of $AsPh_3$, CuI and LiCl.

As it can be seen, the use of mono-Boc aniline (**3.12a**) as well as triflates (**3.12c**), (**3.13b**) and (**3.16**) only lead to disappointing results since none of the conditions tested delivered the corresponding allylic alcohols (entries 1 to 3, 4 to 6, 10 to 12 and 16 to 18, Table 3.1, respectively). More gratifying, di-Boc-bromoaniline (**3.13a**) and *N*-Boc-iodoaniline (**3.14**) proved to be somewhat better substrates for this coupling reaction, delivering the expected allylic alcohols (**3.17**) and (**3.18**) in low (32%) and moderate yield (56%), respectively, (entries 7 to 9 and 13 to 15, Table 3.1, respectively). The better results obtained with the later substrates can probably be ascribed to their less pronounced electronic richness, a feature that is likely to facilitate the oxidative addition of the Pd(0) species into the corresponding carbon-halogen bond.[3.5a,3.14]

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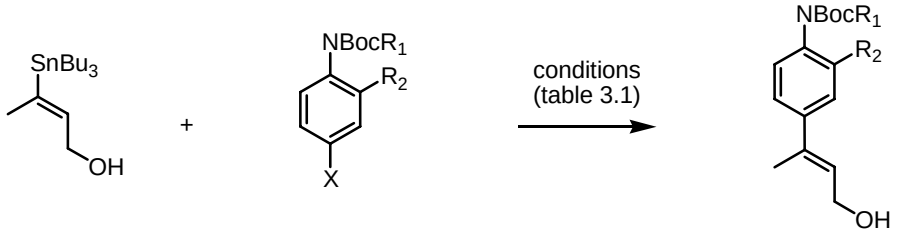
[3.13] Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088.

[3.14] Hegedus, L. S. in "Transition Metals in the Synthesis of Complex Organic Molecules" (2nd edition) **1999**, University Science Books, New York.

**Table 3.1** Stille coupling of enylstannane (**3.11**) and various *N*-Boc anilines.




**3.11** **3.12a**, **3.12c**, **3.13a**, **3.13b**, **3.14** and **3.16** **3.17**: $R_1$ = Boc, $R_2$ = H; **3.18**: $R_1$ = H, $R_2$ = $CO_2Me$

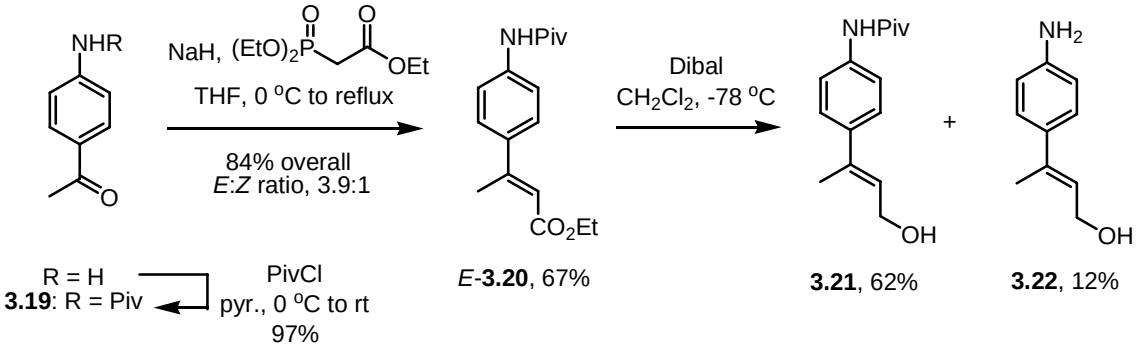
| Entry | *N*-Boc aniline | Conditions[a] | Yield (%) |
|---|---|---|---|
| 1 | **3.12a** | $Pd(PPh_3)_4$, PhH or PhMe, reflux | 0 |
| 2 | X = Br | $Pd_2(dba)_3{\cdot}CHCl_3$ | 0 |
| 3 | $R_1 = R_2 = H$ | $Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, CuI | 0 |
| 4 | **3.12c** | $Pd(PPh_3)_4$ | 0 |
| 5 | X = OTf | $Pd(PPh_3)_4$, LiCl | 0 |
| 6 | $R_1 = R_2 = H$ | $Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, CuI, LiCl | 0 |
| 7 | **3.13a** | $Pd(PPh_3)_4$, PhMe, reflux | 22 |
| 8 | X = Br | $Pd_2(dba)_3{\cdot}CHCl_3$ | 25 |
| 9 | $R_1$ = Boc, $R_2 = H$ | $Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, CuI | 32 |
| 10 | **3.13b** | $Pd(PPh_3)_4$ | 0 |
| 11 | X = OTf | $Pd(PPh_3)_4$, LiCl | Traces[b] |
| 12 | $R_1$ = Boc, $R_2 = H$ | $Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, CuI, LiCl | Traces[b] |
| 13 | **3.14** | $Pd(PPh_3)_4$, PhH or PhMe, reflux | 34 |
| 14 | X = I | $Pd_2(dba)_3{\cdot}CHCl_3$ | 43 |
| 15 | $R_1 = H$, $R_2 = CO_2Me$ | $Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, CuI | 56 |
| 16 | **3.16** | $Pd(PPh_3)_4$ | 0 |
| 17 | X = OTf | $Pd(PPh_3)_4$, LiCl | 0 |
| 18 | $R_1 = H$, $R_2 = CO_2Me$ | $Pd_2(dba)_3{\cdot}CHCl_3$, $AsPh_3$, CuI, LiCl | 0 |

[a] The reactions were performed in NMP at 75 °C-100 °C with 5 mol% of the palladium catalyst, unless otherwise stated. When appropriated, the following amounts of ligands and additives were used: $AsPh_3$ (20 mol %); CuI (15 mol%); LiCl (3 eq.).

[b] As judged by TLC.

In view of the unsatisfactory results obtained in the preparation of allylic alcohols of the type (**3.5**) when using the Stille coupling reaction (*vide infra*, Table 3.1), an alternative approach for this type of compounds was investigated. Accordingly, *para*-aminoacetophenone was treated with PivCl in pyridine to afford the pivalamide (**3.19**) in excellent yield (97%). It is noted that the Piv protecting group is also a strong

directing *ortho*-metallating agent.[3.6,3.15] The crude pivalamide (**3.19**) was subjected to a HWE reaction[3.16] with the sodium salt of trietylphosponoacetate delivering a mixture of the corresponding *α,β*-unsaturated esters (**3.20**) in high yield (84%) and in a 3.9:1 *E*:*Z* ratio. Flash chromatography purification delivered the desired pure *E*-(**3.20**) in 67%, after which it was reduced with Dibal to the allylic alcohol (**3.21**) in moderate yield (62%). Aniline (**3.22**), resulting from over-reduction of *E*-(**3.20**), was also obtained in 12% yield (Scheme 3.6).




**Scheme 3.6** Preparation of allylic alcohol (**3.21**).

## 3.1.1.2 - Preparation of Allylic Alcohol Containing a *para*-Carboxy Phenyl Moiety (Type (3.7))

For convenience, our studies in the *para*-carboxy substitution pattern, *i.e.*, corresponding to allylic alcohols of the type (**3.7**), were conducted using *Z*-(**3.23**).[3.17] Following a procedure by Dvořák and Havránek,[3.18] allylic alcohol *Z*-(**3.23**) was obtained in one pot *via* the hydroalumination of 2-butyn-1-ol with $LiAH_4$ followed by a Pd-catalysed coupling with methyl iodobenzoate in the presence of $ZnCl_2$. The

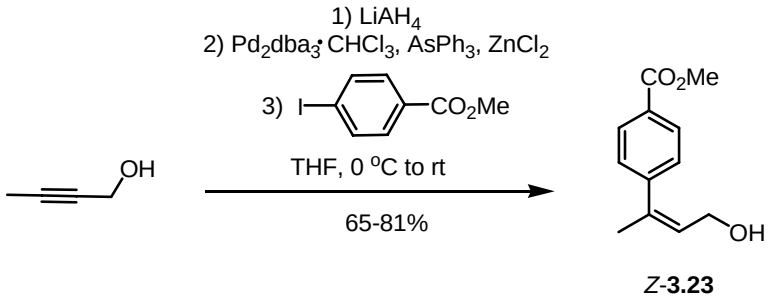
[3.15] For selected examples where the Piv group is used in DoM see: (a) Fuhrer, W.; Gschwend, H. W.; *J. Org. Chem.* **1979**, *44*, 1133. (b) Ho, P.-T. *Can. J. Chem.* **1980**, *58*, 861. (c) Hillis, L. R.; Gould, S. J. *J. Org. Chem.* **1985**, *50*, 718.

[3.16] (a) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. (b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *62*, 1733. For a review see (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1988**, *89*, 863.

[3.17] The preparation of allylic alcohol (*E*)-(**3.23**) has already been reported by Dvořák and Havránek, who obtained this compound in 53% *via* the stereospecific Stille cross-coupling reaction between enylstannane (**3.11**) and methyl para-iodobenzoate. See: Havránek, M.; Dvořák, D. *Collect. Czech. Chem. Commun.* **2000**, *65*, 434.

[3.18] Havránek, M.; Dvořák, D. *J. Org. Chem.* **2002**, *67*, 2125.

reaction proceeded stereoselectively affording (*Z*)-(**3.23**) in good yield (65% to 81%) (Scheme 3.7).



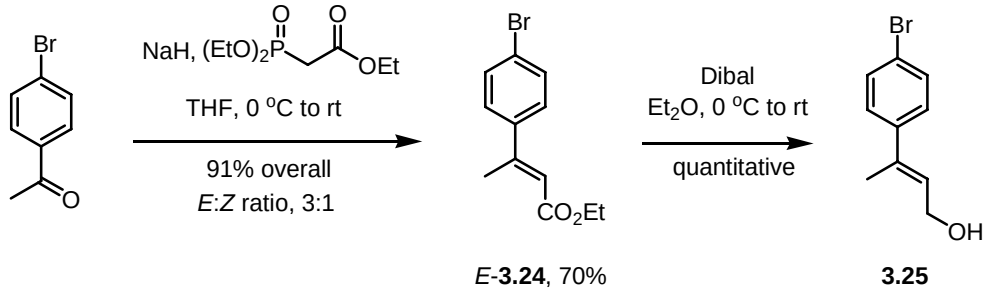

**Scheme 3.7** Preparation of allylic alcohol (*Z*)-(**3.23**).

## 3.1.1.3 - Preparation of Allylic Alcohols Containing a *para*-Halogen Phenyl Moiety (Types (3.8) and (3.9))

Allylic alcohols with a *para*-halogented phenyl moiety, *i.e.*, of the type (**3.8**) and (**3.9**), were planned to be accessed by means of a HWE reaction[3.16] of the corresponding *para*-bromoacetophenones (*i.e.*, X = Br).[3.19] The bromine was chosen due to the versatility that it offers for further functionalization as it is both well suited to participate in metal catalysed cross-coupling[3.4] and halogen-metal exchange reactions.[3.14]

For the preparation of allylic alcohol (**3.25**), *para*-bromoacetophenone was subjected to a HWE reaction[3.16] with the sodium salt of triethyl phosphoacetate affording a *E*:*Z* mixture of the corresponding *α*,*β*-unsaturated esters (**3.24**), in a 3:1 ratio, respectively, which could be separated by flash chromatography. The desired isomer *E*-(**3.24**) was obtained in good yield (70%). Dibal reduction of the later proceeded uneventfully, affording the corresponding allylic alcohol (**3.25**) quantitatively (Scheme 3.8).

[3.19] For a related example see: Martín, R. M.; Islas, G.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **2001**, *57*, 6367.



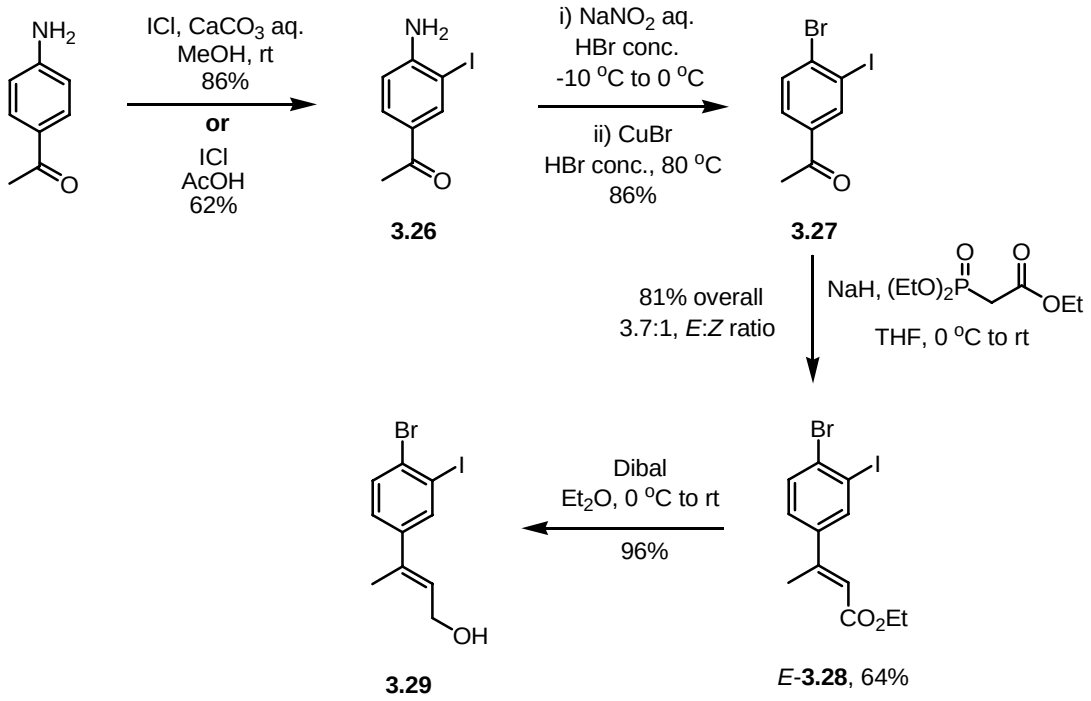

*E*-**3.24**, 70% **3.25**

**Scheme 3.8** Preparation of allylic alcohol (**3.25**).

The more functionalized version, allylic alcohol (**3.29**), was prepared by the sequence shown in Scheme 3.9. The choice of iodine was driven essentially by the anticipated need to differentiate between the two halogen-substituted aromatic positions later on in the synthesis. In addition, iodine offers the same type of versatility as provided by bromine.

Following a literature procedure,[3.20] *para*-aminoacetophenone was treated with ICl in presence of $CaCO_3$ to afford the corresponding iodinated aniline (**3.26**) in good yield (86%). The same transformation could also be accomplished, although in lower yield (62%) by using ICl with AcOH. Once the amino group fulfilled its activating role, amine-halogen exchange was accomplished under Sandmeyer conditions[3.21] ($NaNO_2$ under acidic conditions, followed by CuBr) to afford dihalogenated acetophenone (**3.27**) in high yield (86%). A HWE reaction[3.16] with the sodium salt of trietylphosponoacetate delivered a mixture of the corresponding $\alpha,\beta$-unsaturated esters (**3.28**) in good yield (81%) and in a 3.7:1 ratio, in favour of the desired *E*-(**3.28**). The double bond isomers could be separated by flash chromatography, allowing the isolation of pure *E*-(**3.28**) in 64% yield. Reduction of the ester functionality with Dibal delivered allylic alcohol (**3.29**) in excellent yield (96%).

[3.20] Fujita, K.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785.
[3.21] (a) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633. For related examples see: (b) Sugaya, T.; Mimura, Y.; Kato, N.; Ikuta, M.; Mimura, T.; Kasai, M.; Tomioka, S. *Synthesis* **1994**, 73. (c) Kosuge, T.; Isida, H.; Inaba, A.; Nukaya, H. *Chem. Pharm. Bull.* **1985**, *33*, 1414.




**Scheme 3.9** Preparation of allylic alcohol (**3.29**).

## 3.1.2 - Evaluation of the Relevant Substitution Patterns

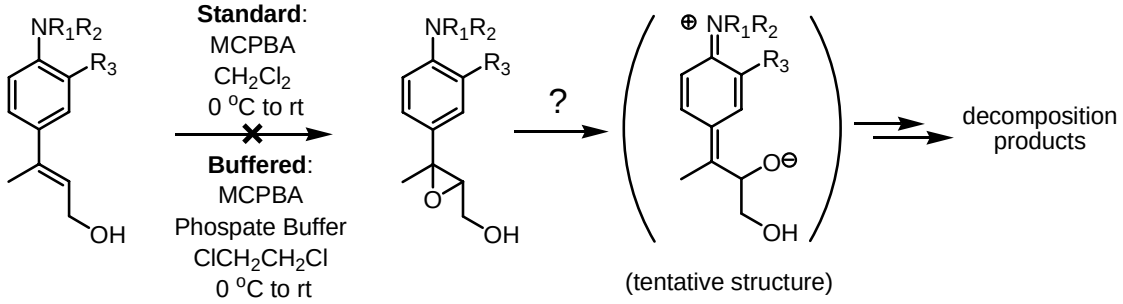
The allylic alcohols (**3.17**), (**3.18**), (**3.21**), *Z*-(**3.23**), (**3.25**) and (**3.29**) were then evaluated as potential starting materials for accessing the all-carbon quaternary stereocenter. For converting these allylic alcohols into the substrates for the Jung rearrangement, *i.e.*, the corresponding vinyl epoxides, the following sequence of reactions was used:[3.1] i) epoxidation of the allylic double bond with MCBPA (as an expedient achiral alternative to the Sharpless epoxidation); ii) Swern oxidation[3.22] of the epoxy-alcohol into the corresponding epoxy-aldehyde; iii) Wittig olefination[3.16c,3.23] into the corresponding vinyl epoxide; and iv) $BF_3 \cdot Et_2O$ promoted Jung rearrangement.[3.1,3.24]

[3.22] (a) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329. (b) Huang, S. L.; Omura, K.; Swern, D. Synthesis **1978**, *4*, 297.

[3.23] (a) Wittig, G.; Schölkopf, U. *Ber. Dtsch. Chem. Ges.* **1954**, *87*, 1318. For selected reviews see: (b) Murphy, P.J.; Brennan, J. *Chem. Soc. Rev.* **1988**, *17*, 1. (c) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1.

[3.24] For a review on the acid catalyzed rearrangements of epoxides see: Rickborn, B. in "Comprehensive Organic Synthesis" (Trost, B. M., Fleming, I. ed.) **1991**, *3*, 733, Pergamon, New York.

MCPBA-epoxidation of *N*-Boc-amino allylic alcohols (**3.17**), (**3.18**) and (**3.21**) failed to deliver the corresponding epoxy alcohols (**3.30**), (**3.27**) and (**3.32**). To rule out the possibility that this outcome was a consequence of the acidic conditions of the reaction medium, allylic alcohols (**3.17**), (**3.18**) and (**3.21**) were also subjected to MCPBA epoxidation in the presence of a phosphate buffer (pH 8)[3.25] (*i.e.*, "buffered conditions") (Scheme 3.10). Disappointedly, the reactions outcome remained unchanged. These findings suggested that epoxides with a 1,4-*N*-Boc/Piv-phenyl moiety are too labile to be manipulated, presumably because of direct conjugation between the electron releasing amino group and the oxirane ring. Therefore the *para*-amino substitution pattern was abandoned.



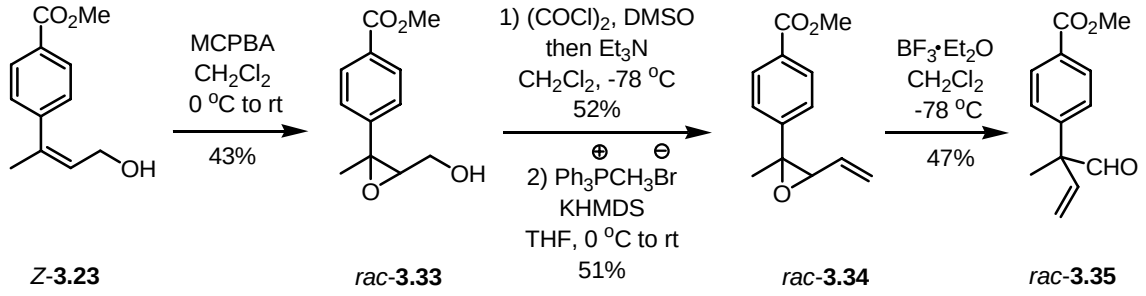

**3.17**: $R_1 = R_2 = Boc$, $R_3 = H$
**3.18**: $R_1 = Boc$, $R_2 = H$, $R_3 = CO_2Me$
**3.21**: $R_1 = Piv$, $R_2 = H$; $R_3 = H$

**3.30**: $R_1 = R_2 = Boc$, $R_3 = H$
**3.31**: $R_1 = Boc$, $R_2 = H$, $R_3 = CO_2Me$
**3.32**: $R_1 = Piv$, $R_2 = H$; $R_3 = H$

**Scheme 3.10** (Attempted) MCPBA epoxidation of allylic alcohols (**3.17**), (**3.18**) and (**3.21**).

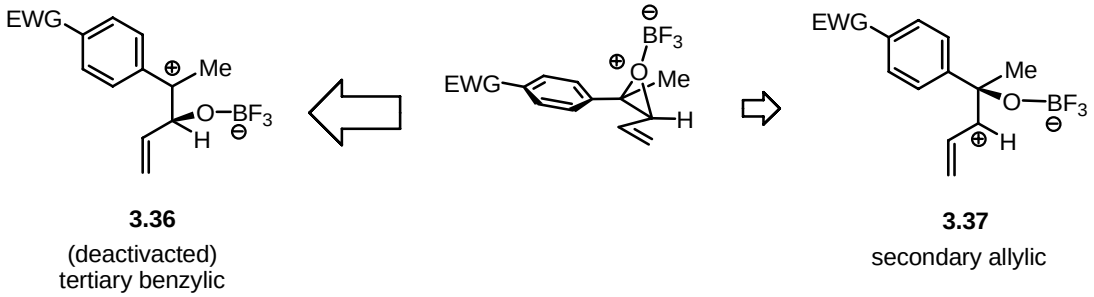
Better results were obtained with the allylic alcohol *Z*-(**3.23**) (Scheme 3.11). MCPBA epoxidation of the later delivered epoxy-alcohol *rac*-(**3.33**) as an oil, although only in modest yield (43%). Swern oxidation[3.22] then produced the corresponding epoxy-aldehyde in 52% yield which was then converted into vinyl-epoxide *rac*-(**3.34**) *via* a Wittig reaction[3.23] with methyltriphenylphosphonium ylide, prepared *in situ* from methyltriphenylphosphonium bromide and KHMDS. Treatment of vinyl-epoxide *rac*-(**3.34**) with $BF_3 \cdot Et_2O$ at -78 °C[3.1] afforded, as the sole product, the desired quaternary aldehyde *rac*-(**3.35**) in moderate yield (47%).

[3.25] Imuta, M.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 1351.




**Scheme 3.11** Conversion of allylic alcohol *Z*-(**3.23**) into quaternary aldehyde *rac*-(**3.35**).

Two important corollaries can be taken from this result: firstly that even a deactivated tertiary benzylic carbocation (**3.36**) is favoured over the alternative secondary allylic (**3.37**) (Scheme 3.12); secondly, that the installation of the desired benzylic quaternary carbon *via* vinyl migration in this type of substrates is a feasible process.

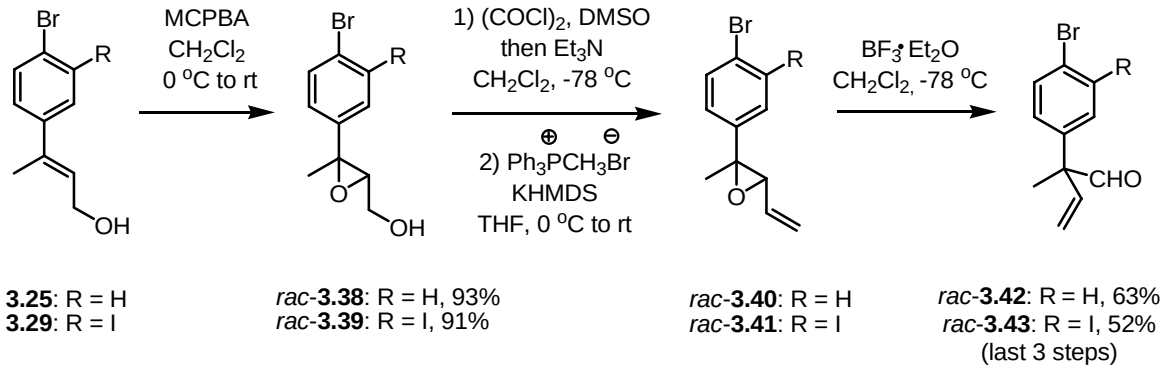



**Scheme 3.12** Comparison between a (deactivated) tertiary benzylic (**3.36**) and a secondary allylic carbocation (**3.37**).

Gratifyingly, similar results were obtained with the halogenated allylic alcohols (**3.25**) and (**3.29**) (Scheme 3.13). Suspecting that the labile nature of this type of substrates was responsible for the low yields previously obtained during the conversion of allylic alcohol (**3.23**) to the corresponding quaternary aldehyde *rac*-(**3.35**) (*vide supra*, Scheme 3.11), it was decided to use the crude products directly into the next step.[3.26] MCPBA epoxidation afforded the crystalline epoxy alcohols *rac*-(**3.38**) and *rac*-(**3.39**) in high yields (93% and 91%, respectively) which, under Swern conditions,[3.22] were oxidized to the corresponding epoxy-aldehydes. Wittig olefination[3.23] at -78 °C using the ylide prepared *in situ* from methyltriphenylphosphonium bromide and KHMDS, afforded the vinyl epoxides *rac*-(**3.40**) and *rac*-(**3.41**). After a rapid

[3.26] The labile nature of 2,3-epoxy-3-phenylbutan-1-ol type substrates has previously been noted to be detrimental to their isolation, see: Coghlan, D. R.; Hamon, P. G. D.; Massy-Westropp, R. A.; Slobedman, D. *Tetrahedron: Asymmetry* **1990**, *1*, 299.

filtration through a short column of silica gel to remove most of the $Ph_3P(O)$, the latter vinyl epoxides were treated with $BF_3{\cdot}Et_2O$ at -78 °C.[3.1] We were happy to find that, in both cases, the desired quaternary aldehydes *rac*-(**3.42**) and *rac*-(**3.43**) were obtained as the only products in 63% and 52% yields over the last three steps, respectively. It is noted that these overall yields correspond to an average yield of 86% and 80% *per* step, respectively.




**Scheme 3.13** Conversion of allylic alcohols (**3.25**) and (**3.29**) into quaternary aldehydes *rac*-(**3.42**) and *rac*-(**3.43**).

In spite of the encouraging results obtained with allylic alcohol *Z*-(**3.23**) (*vide supra*, Scheme 3.11), we decided to focus our attention on allylic alcohols containing a *para*-bromophenyl moiety, namely allylic alcohols (**3.25**) and (**3.29**). This decision was based on the higher yields obtained with the latter substrates (*vide supra*, Scheme 3.11 *vs.* Scheme 3.13) and, perhaps more importantly, on the crystalline nature of epoxy alcohols *rac*-(**3.38**) and *rac*-(**3.39**) and of quaternary aldehydes *rac*-(**3.42**) and *rac*-(**3.43**). The highly crystalline nature of these compounds was anticipated to be important since, in case of need, recrystallization would be a convenient way to increase the enantiopurity of these intermediates.

## 3.1.3 - Enantioselective Formation of the Quaternary Stereocenter

Having established that the all-carbon quaternary centre characteristic of the teleocidins A alkaloids can be accessed, in racemic form, *via* vinyl migration from a conveniently substituted *para*-bromophenyl vinyl epoxide (*vide supra*, Scheme 3.13), we then moved on to investigate the enantioselective version of this process.

Since the quaternary centre was planned to be installed by means of a chirality transfer process from a chiral epoxide, the enantiopurity of the latter is critical and this was the first issue to be addressed.

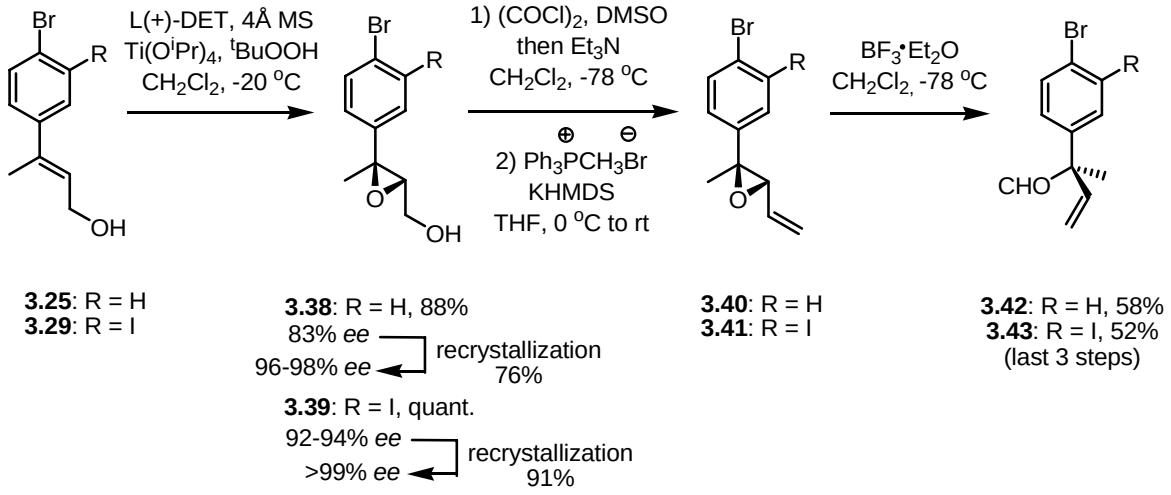
The catalytic Sharpless-Katsuki asymmetric epoxidation[3.27] of allylic alcohols (**3.25**) and (**3.29**) delivered the desired epoxy alcohols (*S*,*S*)-(**3.38**) and (*S*,*S*)-(**3.39**) in good yield (88% and quantitatively, respectively) and with high enantiomeric excess (83% *ee* and 92-94% *ee*, respectively),[3.28] as determined by chiral HPLC (Scheme 3.14). The use of DIP as an alternative to DET as the source of chirality in these reactions did not lead to any improvement in the optical purity. Fortunately, one recrystallization from hexane:ether produced epoxy alcohols (**3.38**) and (**3.39**) with an enhanced enantiomeric excess of 96-98% and >99%, respectively.

Having secured that epoxy alcohols (**3.38**) and (**3.39**) could be prepared with high enantiopurity, the latter were then subjected to the conditions previously used in the racemic series to access the quaternary aldehyde (**3.42**) and (**3.43**) (*vide supra*, Scheme 3.13).

Accordingly, Swern oxidation[3.22] of (**3.38**), followed by Wittig methelenation[3.23] afforded optically pure vinyl epoxide (**3.40**) which upon treatment with $BF_3 \cdot Et_2O$[3.1] delivered the quaternary aldehyde (**3.42**) in good yield (58%, based on allylic epoxide (**3.38**), *i.e.*, with an average of 83% *pe*r step). Similarly, quaternary aldehyde (**3.43**) was also prepared from enantiopure epoxy alcohol (**3.39**) in 52% overall yield (*i.e.*, in an average of 80% *per* step) (Scheme 3.14). Whereas quaternary aldehyde (**3.42**) could be stored neat under argon at low temperature, aldehyde (**3.43**) proved to be less stable and was best kept frozen in a benzene matrix under argon.

[3.27] (a) Gao, Y.; Hanson, M.; Klunder, J. M.; Ko, S. Y.; Masumane, Sharpless, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 5765. For a comprehensive review see (b) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

[3.28] For examples of Sharpless-Katsuki asymmetric epoxidation of similar substrates see: (a) Takano, S.; yanase, M.; Sugihara, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1538. (b) Hamon, D. P. G.; Massy-Westropp, R. A.; Newton, J. L. *Tetrahedron* **1995**, *51*, 12645. (c) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544.s




**Scheme 3.14** Preparation of optical active quaternary aldehydes (**3.42**) and (**3.43**) from allylic alcohols (**3.25**) and (**3.29**), respectively.

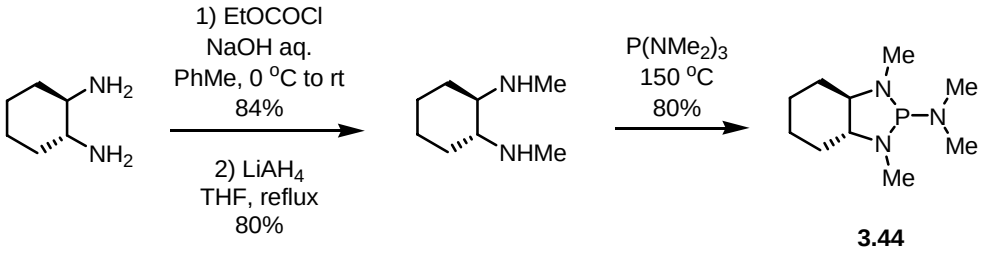
Unfortunately, our attempts to determine the enantiomeric excess of aldehydes (**3.42**) and (**3.43**) by chiral HPLC, and thus conclude about the stereospecificity of the respective Jung rearrangements, only lead to disappointing results as we could not observe any peak separation in the racemic series.

Consequently, it was decided to determine the enantiomeric excess of chiral aldehydes (**3.42**) and (**3.43**) by means of chemical derivatization. Among the different reagents available for such purpose,[3.29] we chose to use the optically active (dimethylamino)tetrahydro-1.3.2-diazaphosphole (**3.44**), often called Alexakis reagent,[3.30] which had already been reported to be efficient in the determination of the optical purity of hindered primary alcohols.[3.1] The Alexakis reagent (**3.44**) was prepared according to the sequence shown in Scheme 3.15. Treatment of (*R*,*R*)-cyclohexane-1,2-diamine with ethylchloroformate afforded the corresponding dicarbamate, which was reduced with $LiAH_4$ to (*R*,*R*)-cyclohexane-1,2-dimethylamine. Upon reaction with $P(NMe_2)_3$, the latter diamine delivered the

[3.29] (a) For a general discussion see: Morrison, J. D. in "Asymmetric Synthesis" **1983**, *Vol I*, Academic Press, New York. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1963**, *34*, 2543. (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (d) Feringa, B. L.; Smaardijk, A.; Wynberg, H. *Tetrahedron Lett.* **1986**, *27*, 997. (e) Strigteveen, B.; Feringa, B. L.; Kellog, R. M. *Tetrahedron* **1987**, *43*, 123. (f) Johnson, C. R.; Elliot, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5019. (g) Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304.

[3.30] (a) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224. (b) Alexakis, A.; Chauvin, A.-S.; Stouvenel, R.; Vrancken, E.; Mutti, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *12*, 1171. (c) Alexakis, A.; Mutti, S.; Normant, J. F.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 437.

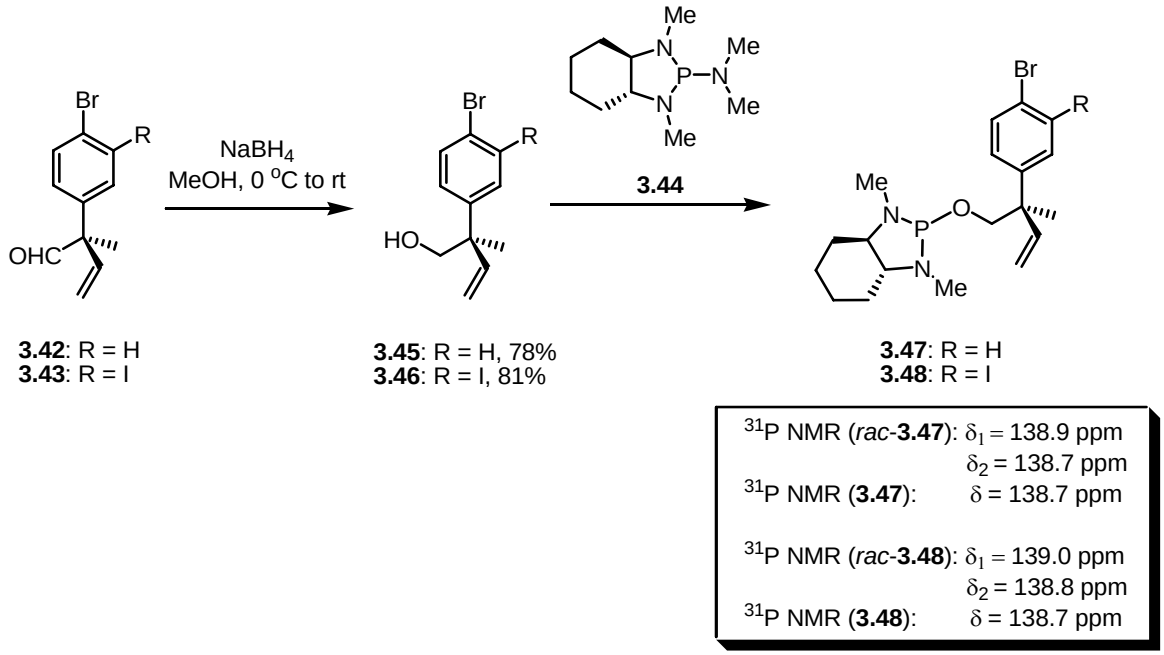
sensitive Alexakis reagent (**3.44**) in good overall yield, which was best kept frozen in a benzene matrix under argon.




**Scheme 3.15** Preparation of the Alexakis reagent (**3.44**).

In order to be derivatized, quaternary aldehydes (**3.42**) and (**3.43**) were first converted into the corresponding primary alcohols (**3.45**) and (**3.46**)[3.31] by reduction with $NaBH_4$, which proceeded in good yields (78% and 81%, respectively). When alcohol *rac*-(**3.45**) was allowed to react with the Alexakis reagent (**3.44**) and the $^{31}$P-NMR of the resulting alkoxytetrahydro-1.3.2-diazaphosphole derivative *rac*-(**3.47**) was recorded, two peaks with the same intensity, at $\delta$ = 138.9 ppm and $\delta$ = 138.7 ppm, corresponding to the two diastereoisomers, were observed. On the other hand, when the same procedure was applied to the optically active (**3.45**), only the higher field peak, at $\delta$ = 138.7 ppm, was present. A similar result was obtained for *rac*-(**3.46**) and (**3.46**): whereas the $^{31}$P-NMR of *rac*-(**3.48**) showed two peaks at $\delta$ = 139.0 ppm and $\delta$ = 138.8 ppm, for the optical active (**3.48**) only a peak at $\delta$ = 138.7 ppm was present. These results imply that the Jung rearrangement of vinyl epoxides (**3.40**) and (**3.41**) into quaternary aldehydes (**3.42**) and (**3.43**), respectively, proceeded in an enantiospecific manner. Thus, the enantiomeric compositions of (**3.42**) and (**3.43**) are > 95% *ee*.

[3.31] Attempts to determine the enantiomeric composition of alcohols (**3.45**) and (**3.46**) by chiral HPLC also failed as no peak separation was observed in the racemic series.




**Scheme 3.16** Determination of the enantiomeric composition of alcohols (**3.45**) and (**3.46**) *via* derivatization with the Alexakis reagent (**3.44**).

## 3.2 - Construction of the Indole Nucleus

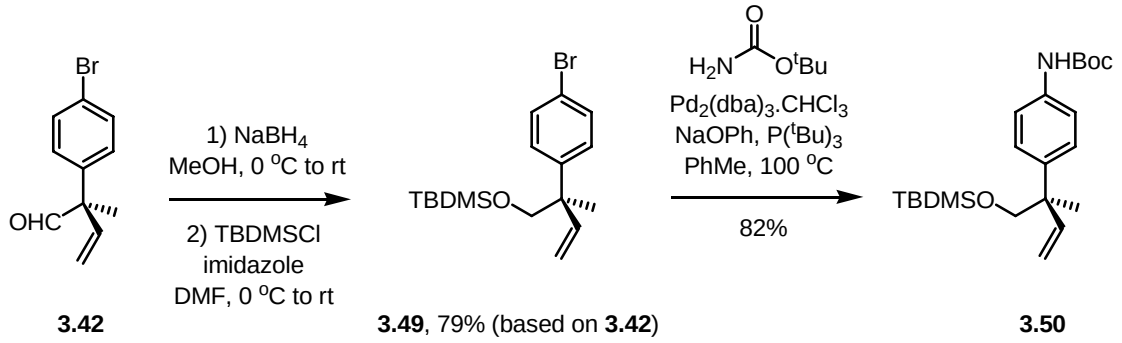
Having secured that the all-carbon quaternary centre could be accessed in an enantioselective manner, we then attended to the construction of the indole nucleus.

### 3.2.1 - Studies Towards Construction of the Indole Nucleus Based on Quaternary Aldehyde (3.42)

Regarding construction of the indole nucleus from quaternary aldehyde (**3.42**), we began by installing the amino functionality corresponding to the *N*-methyl amino group at C-4 in lyngbyatoxin A (Scheme 3.17). The quaternary aldehyde (**3.42**) was first treated with $NaBH_4$ and the crude alcohol obtained was reacted with TBDMSCl in the presence of imidazole[3.32] affording the corresponding TBDMS ether (**3.49**) in good overall yield (79%). The latter was then subjected to a Buchwald-Hartwig amination[3.4] using *tert*-butylcarbamate in the presence of $Pd_2(dba)_3.CHCl_3$ complex, $P(^tBu)_3$ and freshly prepared NaOPh.[3.4d] Gratifying, not only was *N*-Boc aniline (**3.50**)

[3.32] Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

obtained in good yield (82%) but this key reaction could be reproduced on a multigram scale.




**Scheme 3.17** Preparation of *N*-Boc aniline (**3.50**).

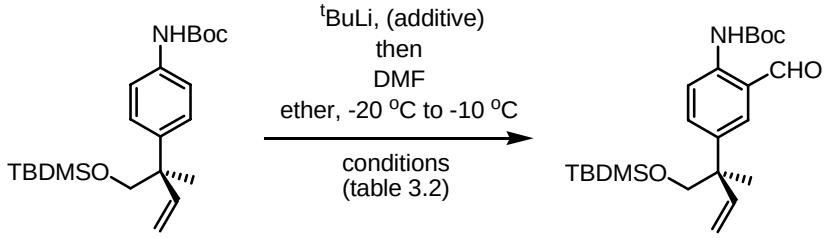
Our annulation strategy calls for a benzaldehyde derivative (*vide* Chapter 2) and the required formyl group was planned to be accessed *via* DoM methodology[3.6] using the newly installed *N*-Boc amino group as the directing metallating agent.[3.7]

Somewhat unexpectedly, however, this step proved to be non-trivial. When *N*-Boc aniline (**3.50**) was subjected to the original conditions developed by Muchowski and Venuti for this type of transformation (*i.e.*, addition of 2.4 eq. of $^{t}$BuLi to a 8% solution of (**3.50**) in THF at -78 °C, stirring for 2½ h at -20 °C, followed by addition of a DMF solution in THF),[3.7a] the $^{1}$H-NMR of the product crude revealed that the reaction had proceeded only with a very low conversion, affording a 6.7:1 ratio of (**3.50**):(**3.51**) (entry 1, Table 3.2).

This disappointing result prompted us to investigate conditions that would lead to an improvement in the reaction outcome. In particular, variables such as the reaction solvent, the use of additives and the amount of the lithiating agent were considered.[3.33,3.34] The most relevant results obtained are present in Table 3.2.

[3.33] The organolithium base is also an important variable in these type of DoM processes. Although there are several examples in the literature where $^{s}$BuLi or even $^{n}$BuLi are used as alternatives to $^{t}$BuLi in the directed ortho metallation of *N*-Boc anilines, invariable in theses cases the aryl substrate undergoing lithiation contains either an electron withdrawing group (see refs. 3.34a to 3.34c) or a second, cooperative, metallating-directing group (see ref. 3.34d). In addition, it has been reported that with $^{n}$BuLi (with or without added TMEDA) or $^{s}$BuLi in THF-hexane, the dilithiation of *N*-Boc-aniline does not proceed even after several hours at room temperature (see refs. 3.7). Therefore, we focused exclusively on the use of $^{t}$BuLi as the base.

**Table 3.2** Directed-*ortho* formylation of (**3.50**).



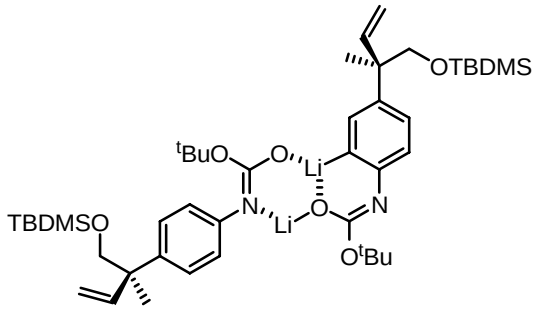

**3.50** **3.51**

| Entry | Conditions | | | | |
|---|---|---|---|---|---|
| | $^t$BuLi (eq.) | TMEDA (eq.)[a] | DMF (eq.) | (**3.50**):(**3.51**) ratio[b] | Yield of (**3.51**) (%)[c] |
| 1[d] | 2.4 | - | 6 | 6.7:1 | ni |
| 2 | 2.4 | - | 6 | 1:1.3 | ni |
| 3[e] | 3.0 | 2.0 | 5 | only (**3.50**) | 0 |
| 4[f] | 3.0 | 2.0 | 5 | 8:1 | ni |
| 5[f] | 3.0 | 0.2 | 5 | 1:2 | ni |
| 6 | 3.0 | 0.5 | 5 | 1:2 | ni |
| 7 | 3.0 | - | 6 | 1:2.6 | 4.7 |
| 8 | 5.0 | - | 12 | 1:10 | 53 |
| 9 | 5.2 | - | 12 | only (**3.51**) | 58 |
| 10 | 5.5 | - | 12 | only (**3.51**) | 59 |
| 11[g] | 5.2 | - | 1.1 | -[h] | -[h] |
| 12[g] | 5.2 | - | 12 | only (**3.51**) | 57 |

[a] "-" stands for "no TMEDA" added;
[b] $^1$H-NMR ratio;
[c] "ni" stands for "not isolated";
[d] THF was used as the reaction solvent;
[e] TMEDA added before $^t$BuLi;
[f] TMEDA added adter $^t$BuLi;
[g] 20 eq. of MeI added after DMF;
[h] a complex mixture was obtained.

[3.34] For selected examples where other bases than $^t$BuLi are used in DoM of *N*-Boc anilines, see: (a) Frank, K. E.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 655. (b) Thornton, T. J.; Jarman, M. *Synthesis* **1990**, 295. (c) Hewawasam, P.; Meanwell, N. A. *Tetrahedron Lett.* **1994**, *35*, 7303. (d) Jönsson, S.; Andersson, G.; Fex, T. *J. Med. Chem.* **2004**, *47*, 2075.

Concerning the reaction solvent, Stanetty and Mihovilovic reported that the half-life of $^{t}$BuLi in THF is approximately 42 min..[3.35] Hence, the large amount of unreacted starting material (**3.50**) observed, (entry 1, Table 3.2) could be accounted by the fact that, instead of being available for the desired reactions, a very substantial amount of $^{t}$BuLi was actually consumed by THF. On the other hand, the half-life of $^{t}$BuLi in $Et_2O$ is reported to be 489 min. at -20 $^{o}$C,[3.35] implying that the decomposition of this lithiating agent should be greatly suppressed in this solvent. As expected, a substantial improvement was obtained when the same reaction was performed in $Et_2O$: the obtained conversion was significantly higher, with the desired aldehyde (**3.46**) being now the major product (entry 2, Table 3.2).




**3.52**

**Figure 3.2** Postulated (1:1) aggregate of monoanion:dianion species (**3.52**).

In spite of this encouraging result, a significant amount of the starting *N*-Boc aniline (**3.50**) remained unreacted. This, together with the fact that a (approximately) 1:1 ratio of (**3.50**):(**3.51**) was produced (according to the $^{1}$H-NMR of the crude product), led us to hypothesize that a stable 1:1 aggregate of monoanion:dianion species (**3.52**) was present in solution (Figure 3.2). In this hypothesis, intermolecular chelation to the monoanionic component in (**3.52**) prevents it to coordinate to $^{t}$BuLi, which is a necessary pre-requisite for the ensuing proximal deprotonation to take place. Hence, formation of the dianionic *N*-lithium amide does not occur which ultimately leads to the isolation of starting (**3.50**).

The reactivity of such aggregates can be modified by the addition of chelating additives, such as TMEDA, which presumably break up the lithium aggregates.[3.6,3.36] Hence, the effect of having TMEDA present was next investigated. Initial runs were performed using 2.0 equivalents of TMEDA, but this proved to have only a detrimental effect regardless of the order of addition: either only the starting TBDMS ether (**3.50**) was delivered or only a very small amount of the desired (**3.51**) was formed (entries 3 and 4, Table 3.2, respectively). However, when a sub-stoichiometric

[3.35] Stanetty, P.; Mihovilovic, M. D. *J. Org. Chem.* **1997**, *62*, 1514.
[3.36] For a leading reference see: Wakefield, B. J. in "Chemistry of Organolithium Compounds" **1974**, Pergamon, Oxford.

amount of TMEDA was added (0.2 eq.), an improved ratio of 1:2 (**3.50**):(**3.51**) was obtained (entry 5, Table 3.2). Unfortunately, increasing the amount of TMEDA to 0.5 equivalents gave no further increase in conversion (entry 6, Table 3.2).

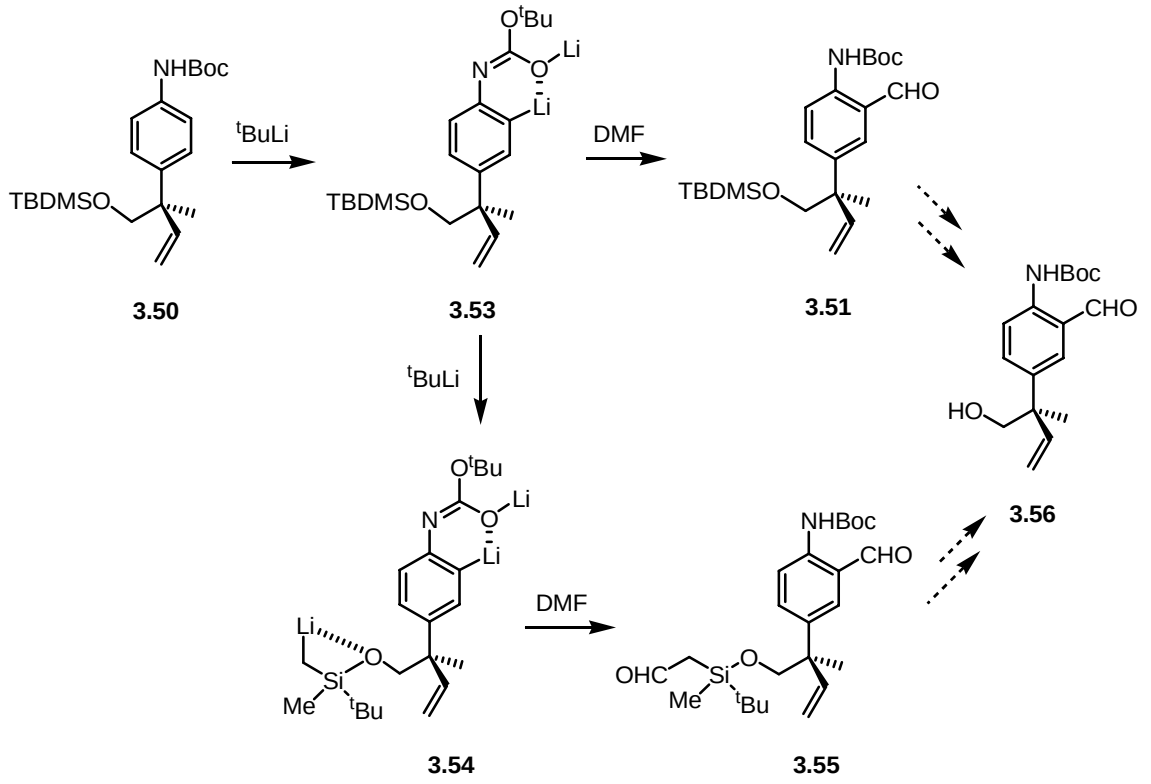
Eventually it was found that the amount of $^{t}$BuLi added was critical for the reaction conversion and that the addition of TMEDA was not essential to obtain complete conversion: when 5.2 equivalents of $^{t}$BuLi were used, (only) the desired benzaldehyde (**3.51**) was isolated in moderate yield (58%) (entry 9, Table 3.2). Increasing the amount of $^{t}$BuLi to 5.5 equivalents did not lead to a significant increase in the isolated yield (entry 10, Table 3.2).

An issue that remained undisclosed at this stage concerned the observation that a considerable excess of $^{t}$BuLi was required for obtaining complete consumption of *N*-Boc aniline (**3.50**). While several possibilities for why such an excess was necessary were considered (*e.g.*, i) that some of the $^{t}$BuLi used remained aggregated as $(^{t}BuLi)_{n}$;[3.37] ii) that it is coordinated by the nucleophilic moieties present in the substrate; iii) that is being consumed by adventitious water; iv) that a stable complex between $^{t}$BuLi and diethyl ether, $(^{t}BuLi{\cdot}2Et_2O)_2$, is being formed[3.38]), none of these satisfactorily explained the irregular relation observed between the conversion of *N*-Boc aniline (**3.50**) and the amount of $^{t}$BuLi added (*e.g.*, compare entries 2, 7 and 8, Table 3.2).

However, when this reaction was scaled-up and the conditions corresponding to entry 10 in Table 3.2 were used, a more convincing explanation emerged. Under these reaction conditions, a more polar by-product, dialdehyde (**3.55**), was isolated in 22% yield (Scheme 3.18). Although the silyl moiety is commonly viewed as an alcohol protecting group that is relatively stable to basic conditions, metallation *α* to silicon is a well-known process.[3.39,3.40] *A posteriori* examination of the TLC plates corresponding to entries 7 to 10 in Table 3.2 suggested that, although it could never

[3.37] Eastham, J. *J. Am. Chem. Soc.* **1964**, *86*, 1076.
[3.38] Bates, T. F.; Clarke, M. T.; Thomas, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5109.
[3.39] For leading references see: (a) Friesen, R. W.; Sturino, C.; F.; Daljeet, A.; K.; Kolaczewska, A. *J. Org. Chem.* **1991**, *56*, 1944. (b) Friesen, R. W.; Trimble, L. A. *J. Org. Chem.* **1996**, *61*, 1165. (c) Peterson, D. J. J. *Organomet. Chem.* **1967**, *9*, 373. (d) MacDonald, J. E.; Pointdexter, G. S. *Tetrahedron Lett.* **1987**, *28*, 1851.
[3.40] For general discussions concerning deprotonations *α* to silicon, see: (a) Colvin, E. W. in "Silicon in Organic Synthesis" **1981**, Butterworths, London. (b) Weber, W. P. in "Silicon Reagents for Organic Synthesis" **1983**, Springer-Verlag, Berlin,.

be isolated, variable amounts of dialdehyde (**3.55**) had been formed in all of these runs. In particular, entries 7 and 8 in Table 3.2, by corresponding to a situation where starting (**3.50**) was recovered, imply that the formation of the desired aryl dianion (**3.53**) occurred in competition with the generation of the anion (**3.54**). It is noted that although dialdehyde (**3.55**) is a by-product, its formation is not completely detrimental. In fact, since the formylated TBDMS protecting group can presumably be cleaved under the same conditions as a "normal" TBDMS,[3.41] the desired benzaldehyde (**3.56**) could equally be accessed from (**3.51**) and (**3.55**).




**Scheme 3.18** Competitive formation of benzaldehydes (**3.51**) and (**3.55**).

Having established conditions to successfully introduce the required formyl functionality, we turned our attention to the methylation of the *N*-Boc aniline (**3.51**). We began by briefly investigating the feasibility of a one pot sequential *C*-formylation/*N*-methylation.[3.42] Because of the existence in solution of anions (**3.53**)

[3.41] Greene, T. W.; Wuts, P. G. M. in "Protective Groups in Organic Synthesis" (3rd edition) **1999**, John Wiley & Sons, New York.

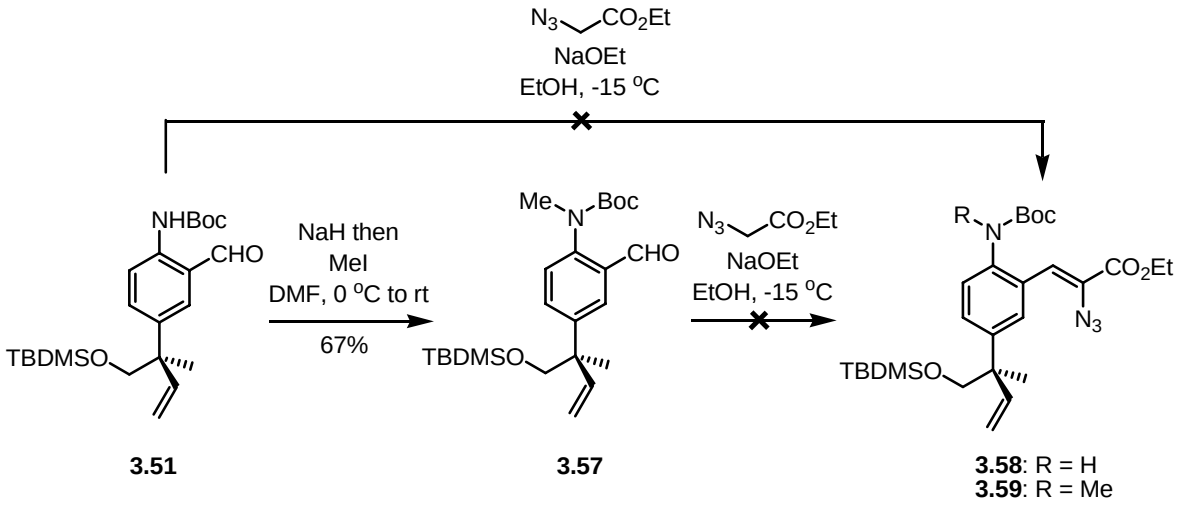
[3.42] Michowski and Venuti already demonstrated that sequential *C*-methylation/*N*-methylation is feasible: these authors were able to obtain *N*-methyl-*N*-Boc-*ortho*-toluidine in high yield by quenching the obtained dianion of *N*-Boc aniline with excess of methyl iodide. See ref. 3.7a.

and (**3.54**) and due to the need of using two different electrophiles, this procedure was anticipated to be complex. Indeed, when aniline (**3.50**) was treated with 5.2 equivalents of $^{t}$BuLi, followed by 1.1 equivalents of DMF[3.43] and finally by an excess of MeI (20 eq.), a very complex mixture of products was obtained (entry 11, Table 3.2). On the other hand, using an excess of both DMF (12 eq.) and MeI (20 eq.), resulted in the isolation of aldehyde (**3.51**) in moderate yield (57%), but none of the desired *N*-methylated product (**3.57**) could be isolated (entry 12, Table 3.2). The preparation of *N*-Boc methyl aniline (**3.57**) was eventually achieved in 67% yield by treating *N*-Boc aniline (**3.51**) with NaH followed by MeI (Scheme 3.19).

The next step in the planned synthetic sequence was the conversion of *N*-Boc benzaldehydes (**3.51**) or (**3.57**) into the corresponding *N*-Boc azidocinnamtes (**3.58**) or (**3.59**), respectively. Unfortunately, and regardless of extensive attempts, we never succeeded at this transformation. Instead a complex mixture was always obtained (Scheme 3.19).

This serious setback prompted us to perform model studies using various protected 2-aminobenzaldehydes. In particular, and suspecting that the Boc protecting group was at the origin of the problem, we were interested in investigating the influence of the amino protecting group in the convertion of protected 2-aminobenzaldehydes into the corresponding azidocinnamates and on the formation of the indole nucleus.

[3.43] The value of 1.1 eq. of DMF corresponds to the theoretical value required to achieve complete *C*-formylation (*i.e.*, in (**3.51**) plus (**3.55**)) and was calculated in the following way: let $n_1$ be the initial number of mole of *N*-Boc aniline (**3.50**) and $n_2$ the theoretical number of mole of DMF necessary to achieve complete *C*-formylation; assuming that the isolated yields of aldehyde (**3.52**) and dialdehyde (**3.55**) correspond to the amounts of dianion (**3.53**) and trianion (**3.54**) in solution and because the later possesses two carbon reactive sites where formylation can take place, it comes that $n_2 = 0.55n_1 + 2\times0.22n_1 = n_1$.



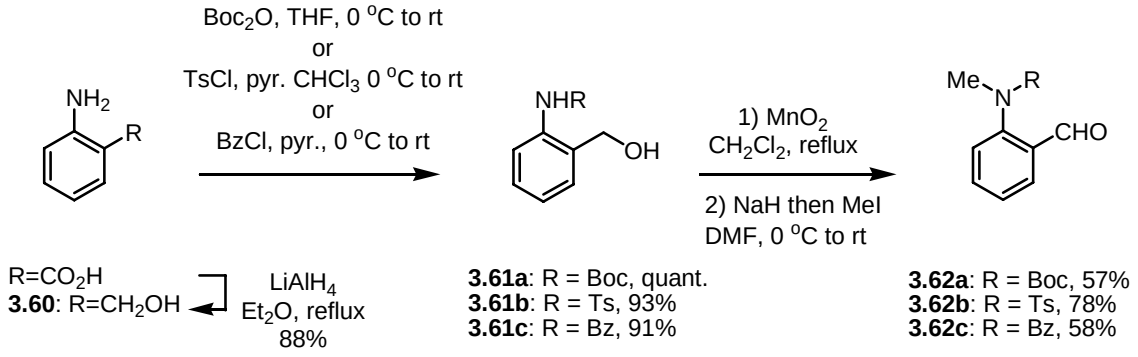

**Scheme 3.19** Preparation of *N*-Boc methyl aniline (**3.57**) and attempted conversion of (**3.51**) and (**3.57**) into vinyl azides (**3.58**) and (**3.59**).

## 3.2.1.1 - Model Studies

For the purpose of the model studies, various 2-aminobenzaldehydes with different amino protecting groups were prepared and the corresponding Hemetsberger indole reactions were investigated.

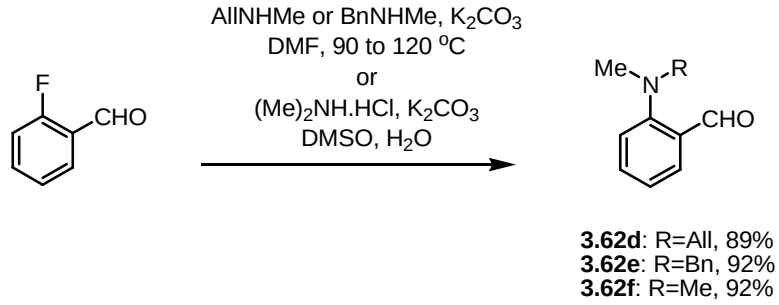
2-Aminobenzaldehydes with an electron withdrawing protecting group at the nitrogen were accessed according to Scheme 3.20. *ortho*-Antharanilic acid was treated with $LiAH_4$ to afford the known benzylic alcohol (**3.60**)[3.44], and the latter was then converted into several *N*-protected anilines. Accordingly, reaction with $Boc_2O$ afforded *N*-Boc aniline (**3.61a**) in quantitative yield, reaction with TsCl delivered *N*-Ts aniline (**3.61b**) in 93% yield and reaction with BzCl in pyridine produced (**3.61c**) in 91% yield. Oxidation of the benzylic alcohols (**3.61a**), (**3.61b**) and (**3.61c**) with freshly prepared $MnO_2$ followed by methylation with MeI delivered the corresponding protected methyl 2-formylanilines (**3.62a**), (**3.62b**) and (**3.62c**) in moderate to good yields (57%, 78% and 58%, respectively, over the last two steps).

[3.44] Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 2548.




**Scheme 3.20** Preparation of *N*-protected 2-aminobenzaldeyhdes (**3.62**).

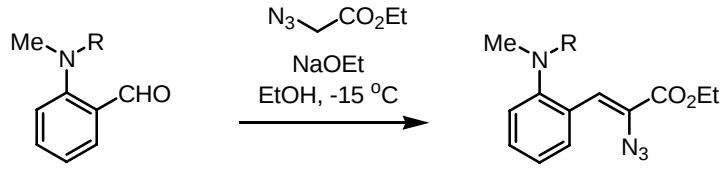
2-Aminobenzaldehydes with a non-electron withdrawing protecting group at the nitrogen were best accessed *via* nucleophilic aromatic substitution of *ortho*-fluorobenzaldehyde with *N*-methylamines (Scheme 3.21). Accordingly, reaction with allylmethylamine, benzylmethylamine and dimethylamine hydrochloride salt in the presence of potassium carbonate afforded methyl 2-formylanilines (**3.62d**), (**3.62e**) and (**3.62f**) in high yields (89%, 92% and 92%, respectively).




**Scheme 3.21** Preparation of *N*-protected 2-aminobenzaldeyhdes (**3.62d**) to (**3.62f**).

The *ortho*-formylated protected anilines (**3.62a**) to (**3.62f**) were then converted into the corresponding 2-azidocinamates (**3.63a**) to (**3.63f**) by reaction with excess of ethyl azidoacetate in freshly prepared ethanolic NaOEt at low temperature (Scheme 3.22). The stereochemistry about the vinyl azide double bond in the azidocinnamates (**3.63a**) to (**3.63f**) is assumed to be *Z*, presumably the more thermodynamically stable isomer. As a general trend, it was found that 2-aminobenzaldehydes containing an electron withdrawing group at nitrogen afforded the corresponding vinyl azides in lower yields and considerable less cleanly than the corresponding substrates with a non-electron withdrawing protecting group at nitrogen. Furthermore, it was also found that the yields for this step were greatly dependent on the work-up procedure adopted. Accordingly, it proved to be important that, after several aqueous washings, the

organic layer was concentrated to approximately 1/4 of its original volume, rapidly filtrated through a short column of silica gel and only then concentrated to dryness.



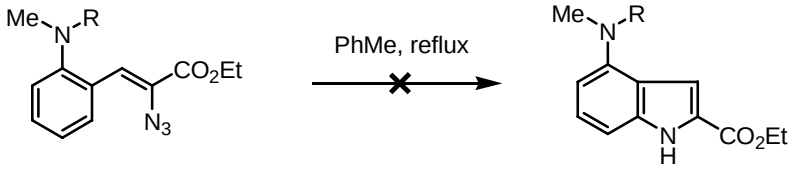

**3.62a**: R = Boc
**3.62b**: R = Ts
**3.62c**: R = Bz
**3.62a**: R = All
**3.62b**: R = Bn
**3.62c**: R = Me

**3.63a**: R = Boc, 35%-53%
**3.63b**: R = Ts, 43%-48%
**3.63c**: R = Bz, 41-49%
**3.63d**: R = All, 69%
**3.63e**: R = Bn, 72%
**3.63f** : R = Me, 65%

**Scheme 3.22** Preparation of ethyl azidocinammates (**3.63a**) to (**3.63f**).

A mild thermolysis of 2-azidocinnamates (**3.63a**) to (**3.63f**) was then performed in refluxing toluene under argon. After some disappointing attempts to purify the crude materials by column flash chromatography, eventually it was found that somewhat better results were obtained by using (repeated) preparative thin layer chromatography.

Invariably, vinyl-azides with an electron withdrawing protecting group at the nitrogen, *i.e.*, Boc-(**3.63a**), Ts-(**3.63b**) and Bz-(**3.63c**), afforded at best very low yields of the corresponding 4-methylaminoindoles (**3.64a**), (**3.64b**) and (**3.64c**) (Scheme 3.23). Instead, a complex mixture of several unidentified by-products was produced.

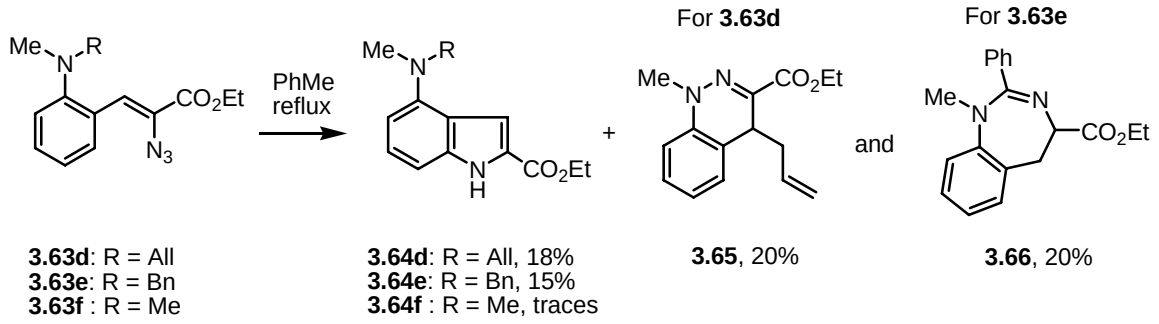



**3.63a**: R = Boc
**3.63b**: R = Ts
**3.63c**: R = Bz

**3.64a**: R = Boc, traces ?
**3.64b**: R = Ts, <5%
**3.64c**: R = Bz, traces ?

**Scheme 3.23** (Attempted) Hemetsberger reaction of ethyl azidocinammates (**3.63a**) to (**3.63c**).

Somewhat better results were obtained with 2-azidocinnamates with a non-electron withdrawing protecting group at the nitrogen, namely All-(**3.63d**) and Bn-(**3.63e**) (Scheme 3.24). Thermolysis of azidocinammate All-(**3.63d**) afforded, after purification by repeated PTLC, the desired indole (**3.64d**) in 18% yield together with dihydrocinnoline (**3.65**) in 20% yield. Similarly, the Hemetsberger reaction of azide Bn-(**3.63d**) delivered the expected indole (**3.64e**) in 15% yield together with benzodiazepine (**3.66**) in 20% yield. A mixture of several unidentified by-products was also produced in these reactions. In contrast, thermolysis of azidocinammate (**3.63f**) only afforded trace amounts of the corresponding indole (**3.64f**) together with a complex mixture of unidentified by-products.




**Scheme 3.24** Hemetsberger reaction of ethyl azidocinammates (**3.63a**) to (**3.63f**).

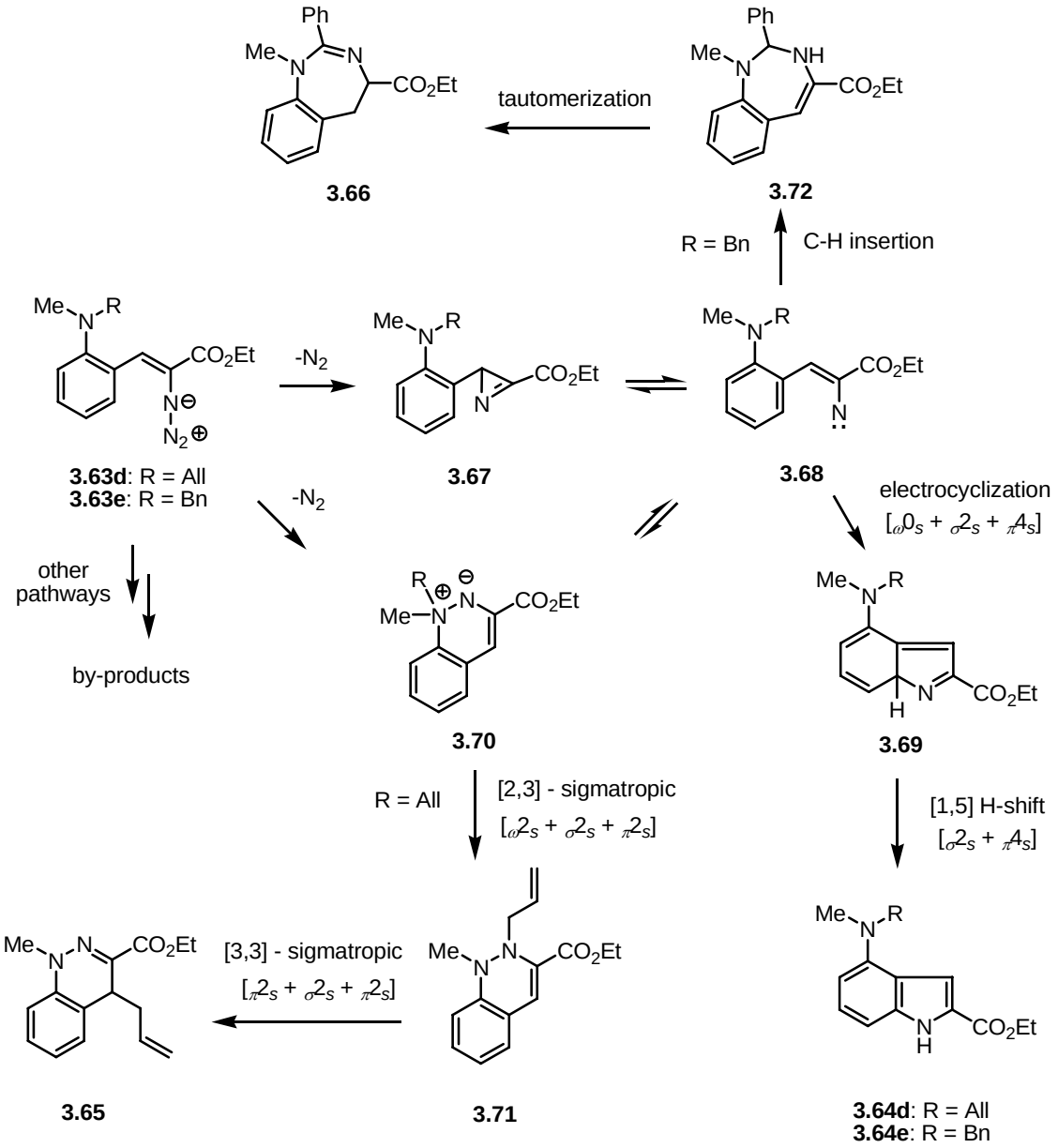
The formation of the (identified) products in these reactions was rationalized according to Scheme 3.25. The thermal decomposition of 2-azidocinammates, *e.g.*, (**3.63d**) and (**3.63e**), typically proceeds with the generation of the 2*H*-azirine (**3.67**),[3.2,3.45] which serves as a reversible source of the reactive singlet nitrene (**3.68**).[3.46] The desired indole carboxylates, *e.g.*, (**3.64d**) and (**3.64e**), are almost certainly formed by electrocyclization of the singlet vinyl nitrenes (**3.68**) into (**3.69**) followed by an aromatising [1,5]-hydrogen shift, a pericyclic sequence that constitutes the core of the Hemetsberger indole synthesis.[3.2] Thermolysis of 2-azidocinammates such as (**3.63d**) and (**3.63e**) can also proceed with the participation of the *ortho*-amino group, in which case the zwitterionic species (**3.70**) is formed.[3.47]

[3.45] (a) Knittel, D.; Hemetsberger, H.; Leipert, R.; Weidmann, H. *Tetrahedron Letts.* **1970**, 1459. (b) Isomura, K.; Okada, M.; Taniguchi, H. *Tetrahedron Letts.* **1969**, 4073 and references therein.

[3.46] Hassner, A.; Wiegand, N. H.; Gottlieb, H. E. *J. Org. Chem.* **1986**, *51*, 3176.

[3.47] For some examples involving cyclic sulphur-nitrogen ylides see: (a) Grant, R. D.; Moody, C. J.; Rees, C. W.; Tsoi, S. C. *J. Chem. Soc. Chem. Commun.* **1982**, 884. (b) Grains, R. S. G.; Grant, R.; Moody, C. J.; Rees, C. W.; Tsoi, S. C. *J. Chem. Soc. Perkin Trans 1* **1986**, 483. (c) Grains, R. S. G.; Grant, R.; Moody, C. J.; Rees, C. W.; Tsoi, S. C. *J. Chem. Soc. Perkin Trans 1* **1986**, 491.

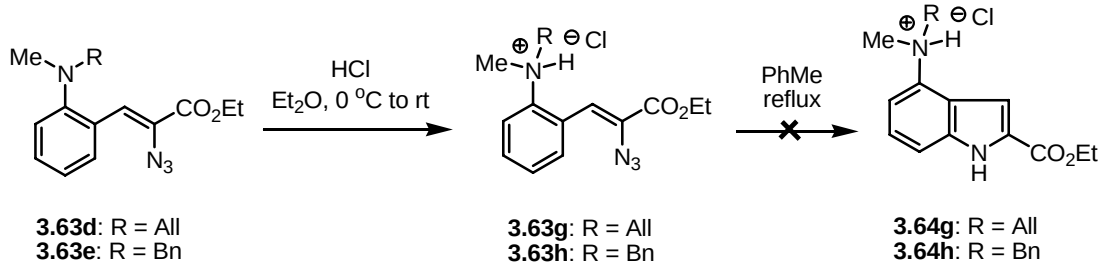
For the case of All-(**3.63d**), a sequence of symmetry-allowed sigmatropic rearrangments involving the allyl group leads to dihydrocinnoline (**3.65**): a [2,3]-allyl shift first affords (**3.71**) which then undergoes a [3,3]-allyl shift (Claisen-Cope type rearrangement) delivering (**3.65**).




**Scheme 3.25** (Proposed) formation of indoles (**3.64d**) and (**3.64e**), dihydrocinnoline (**3.65**) and benzodiazepine (**3.66**).

On the other hand, Bn-(**3.63e**) cannot participate in these types of pericyclic processes. Instead, the corresponding nitrene (**3.68**) (presumably a singlet) undergoes a C-H insertion reaction into the benzylic position[3.48] affording (**3.72**) which then (intermolecularly) tautomarizes into benzodiazepine (**3.66**). Other reaction pathways are likely to be responsible for the formation of the unidentified by-products.

Efforts to avoid the formation of ylide species (**3.70**), and thus to prevent some of the competitive pathways in these processes, were attempted by "tightening up" the nitrogen lone pair. Hence azidocinnamates (**3.63d**) and (**3.63e**) were converted into the corresponding (highly hygroscopic) hydrochloride salts (**3.73a**) and (**3.73b**) by treatment with 2 M HCl/ether solution. The crude salts obtained were subjected to mild thermolysis in refluxing toluene (Scheme 3.26). Disappointedly, only a complex mixture was obtained in both cases.




**3.63d**: R = All
**3.63e**: R = Bn

**3.63g**: R = All
**3.63h**: R = Bn

**3.64g**: R = All
**3.64h**: R = Bn

**Scheme 3.26** (Attempted) preparation of hydrochloride salts (**3.64g**) and (**3.64h**).

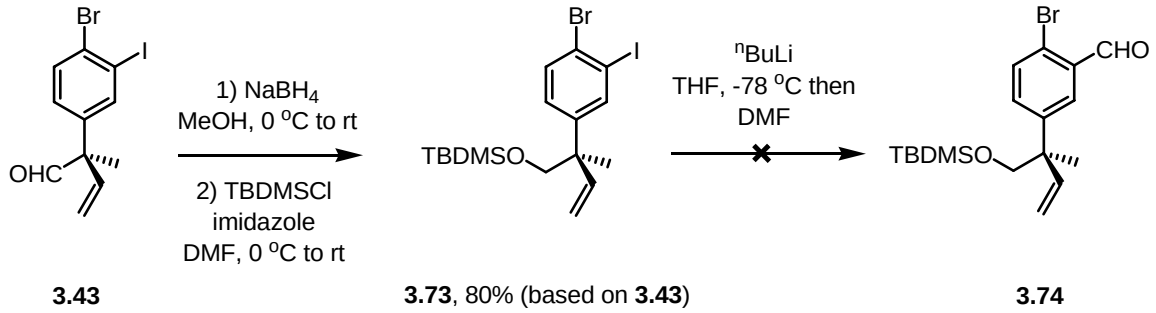
These model studies suggested that the presence of a (protected) amino moiety *ortho* to the vinylnitrene functionality is not compatible with the Hemetsberger-Knittel indole synthesis since the desired indole products, if formed, were always delivered in poor yields. Furthermore, these results imply that construction of the indole nucleus in the Hemetsberger-Knittel sense has to take place *prior* to the installation of the amino functionality. Therefore we concentrated on accessing the indole nucleus from quaternary aldehyde (**3.43**). It is noted that, as a consequence of the more functionalized nature of the phenyl moiety in quaternary aldehyde (**3.43**), the installation of the amino moiety can be delayed to after construction of the indole nucleus.

[3.48] Henn, L.; Hickey, D. M. B.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2189.

## 3.2.2 – Studies Towards the Construction of the Indole Nucleus based on Quaternary Aldehyde (3.43)

The first issue to be addressed when attempting to access the indole nucleus from quaternary aldehyde (**3.43**) concerns the formylation of the C-3a position (indole numbering). This was intended to be achieved *via* a regioselective lithium-iodine exchange followed by trapping the transient lithium species with DMF.

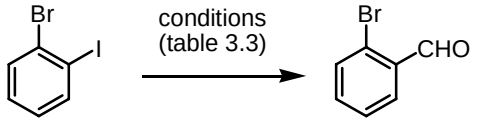
To this end, quaternary aldehyde (**3.43**) was first reduced to the corresponding alcohol with $NaBH_4$ and the crude material obtained was then treated with TBDMSCl in the presence of imidazole[3.32] delivering the silyl ether (**3.73**). Unexpectedly, when the latter was subjected to the standard conditions for formylation *via* metal-halogen exchange (*i.e.*, $^{n}$BuLi, DMF in THF at -78 $^{o}$C) a very complex mixture was obtained with the corresponding $^{1}$H-NMR showing, at best, trace amounts of the desired benzaldehyde (**3.74**) (Scheme 3.27).



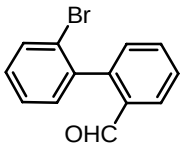

**Scheme 3.27** (Attempted) preparation of benzaldehyde (**3.74**).

This disappointing result prompted us to carry out model studies for this transformation. *ortho*-Iodobromobenzene was used as a surrogate for (**3.43**). The most relevant results obtained are shown in Table 3.3.

**Table 3.3** Studies for the conversion of *ortho*-iodobromobenzene into *ortho*-bromobenzaldehyde.




| Entry | Conditions[a] | Yield (%)[b] |
|---|---|---|
| 1 | i) $^{n}$BuLi, THF, -78 $^{o}$C<br>ii) after t = 2 min., DMF | traces[c] |
| 2 | DMF present at t = 0<br>i) $^{n}$BuLi, THF, -78 $^{o}$C | traces[c] |
| 3 | i) $^{n}$BuLi, $Et_2O$:THF (1:1), -110 $^{o}$C<br>ii) after t = 2 min., DMF | 15%<br>5% of (**3.75**) |
| 4 | DMF present at t = 0<br>i) $^{n}$BuLi, $Et_2O$:THF (1:1), -110 $^{o}$C | 24% |
| 5 | DMF present at t = 0<br>i) $^{n}$BuLi, $Et_2O$:hexane (1:1), -110 $^{o}$C | traces[c] |
| 6 | i) $^{n}$BuLi, PhMe, -100 $^{o}$C<br>ii) after t = 1 min., DMF | 45% |
| 7 | DMF present at t = 0<br>i) $^{n}$BuLi, PhMe, -100 $^{o}$C | 60% |



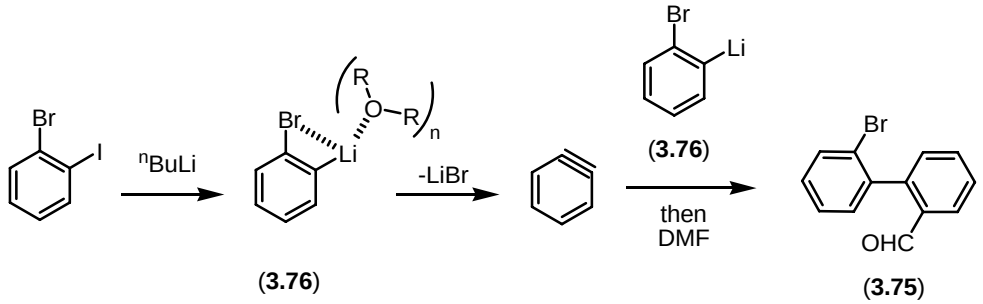

(**3.75**)

[a] 1.05 eq. of $^{n}$BuLi and 2.5 eq. DMF were used;
[b] Isolated yields of *ortho*-bromobenzaldehyde, unless otherwise stated; it is noted that, due to the volatility of *ortho*-bromobenzaldehyde, the reaction yields are probably slightly higher;
[c] As judged by the $^{1}$H-NMR of the crude product obtained.

Performing the reaction in THF at -78 $^{o}$C only led to disappointing results since a complex mixture of products was obtained (entries 1 and 2, Table 3.3). $^{1}$H-NMR analysis of the crude mixtures showed that the expected *ortho*-bromobenzaldehyde was, at best, present in only trace amounts. Somewhat better results were obtained when the reaction was carried in THF:$Et_2O$ (1:1).[3.49] With these conditions, the desired benzaldehyde could be isolated in 15% and 24% yields, depending on the order of addition of DMF (entries 3 and 4, Table 3.3, respectively). Additionally, when the conditions corresponding to entry 3 were used, a compound tentatively assigned as biphenyl (**3.75**) was also isolated, although in very low yield (5%). Formation of the latter was rationalized by means of a benzyne intermediate, thus suggesting that at the origin of the low yields thus far obtained is the short life of the

[3.49] (a) Chen, L. S.; Chen, G. J.; tamborski, C. *J. Organomet. Chem.* **1980**, *193*, 283. (b) Leroux, F.; Sclosser, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4272.

lithiated species (**3.76**) (Scheme 3.28). Furthermore, that the desired *ortho*-bromobenzaldehyde was formed, albeit in low yields, when a less polar solvent was used (*i.e.*, THF:$Et_2O$ (1:1) *vs.* THF) was interpreted in the following way: decomposition of the lithiated (**3.76**) occurs as its solvated complex (by $R_2O$ molecules) *via* concerted elimination of LiBr owing to intramolecular coordination of Br→Li between the *ortho*-disposed Br and Li; less polar solvents will coordinate to lithium less efficiently hence retarding the elimination of LiBr.[3.50]




**Scheme 3.28** Formation of biphenyl (**3.75**) *via* benzyne.

We therefore investigated other less polar solvent systems. The use of $Et_2O$:hexane (1:1) resulted in a complex mixture, presumably due to the low solubility of the lithiated specie (**3.76**) in this solvent system (entry 5, Table 3.3). After considerable experimentation, eventually it was found that by performing the reaction in toluene at approximately -100 °C,[3.51] the competing benzyne formation was comparatively slow and thus the lithiation primary product (**3.76**) could be successfully trapped with DMF. With these conditions the expected benzaldehyde was isolated in 45% yield (entry 6, Table 3.3). A better result was obtained by using Barbier-type conditions, *i.e.*, by adding $^n$BuLi to a solution containing *ortho*-iodobromobenzene and DMF (entry 6, Table 3.3): the *ortho*-bromobenzaldehyde was isolated in 60% yield (entry 7, Table 3.3).

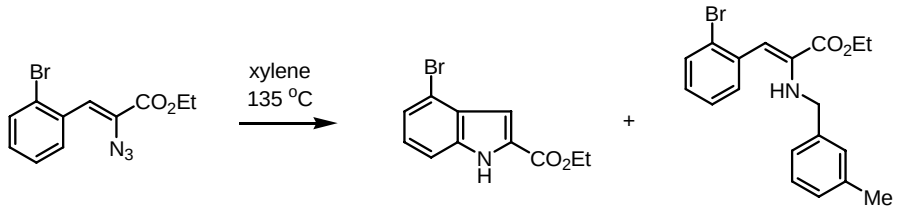
These newly found conditions were then applied to the formylation of the TBDMS ether (**3.73**) (Scheme 3.29). Unexpectedly, when the conditions that delivered the highest yields in the model studies were used, *i.e.*, Barbier-type conditions and performing the reaction in toluene at approximately -100 °C, the desired

[3.50] Nefedov, O. M.; D'yachenko, A. I. *Doklady Akademii Nauk SSSR* **1971**, *198*, 593.

[3.51] Similar conditions for the lithium-iodine exchange of a 2,6-dibromoiodobenzene derivative have been reported recently, see: Yamada, K.; Kurokawa, T.; Tokuyama, H., Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 6630.

benzaldehyde (**3.74**) was obtained in only 15% yield while the starting silyl ether (**3.73**) was recovered in approximately 75% yield. This somewhat surprisingly result implies that the lithium-iodine exchange is considerably slower for the TBDMS ether (**3.73**) than for *ortho*-iodobromobenzene. Fortunately, when the TBDMS ether (**3.73**) was treated with $^{n}$BuLi in toluene at -100 $^{o}$C and DMF was added after approximately 2 minutes, the elusive benzaldehyde (**3.74**) could be obtained in reproducible 65-71% yield. Subsequent condensation with excess of ethyl azidoacetate in freshly prepared ethanolic NaOEt at low temperature afforded vinylazide (**3.77**) in 60 % yield, hence setting the stage for the planned Hemetsberger-Knittel reaction. This was then accomplished by heating (**3.77**) in xylene, cleanly delivering indole (**3.78**) in good yield (69%).[3.52]

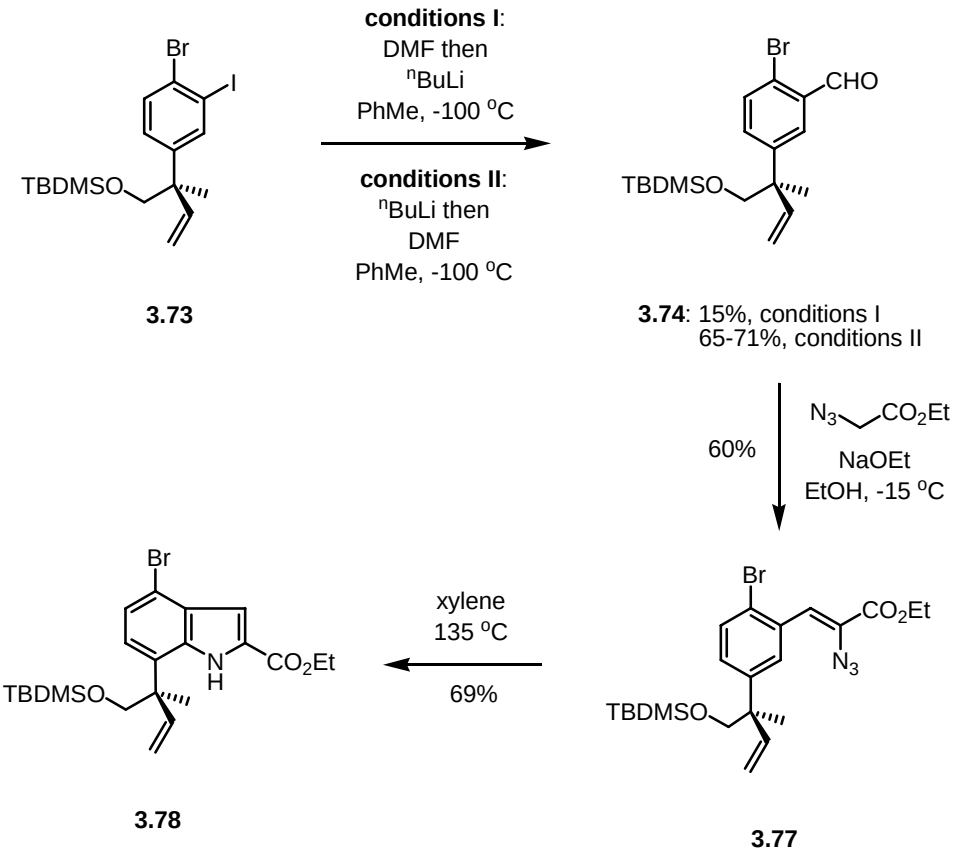
[3.52] Interestingly, thermolysis of the model vinyl azide (**3.79**) afforded the expected indole (**3.79**) together with enamide (**3.81**) in 81% and 8% yields, respectively (Scheme 3.A).




**3.79** **3.80**, 81% **3.81**, 8%

**Scheme 3.A** Thermolysis of model azidocinnamate (**3.79**).

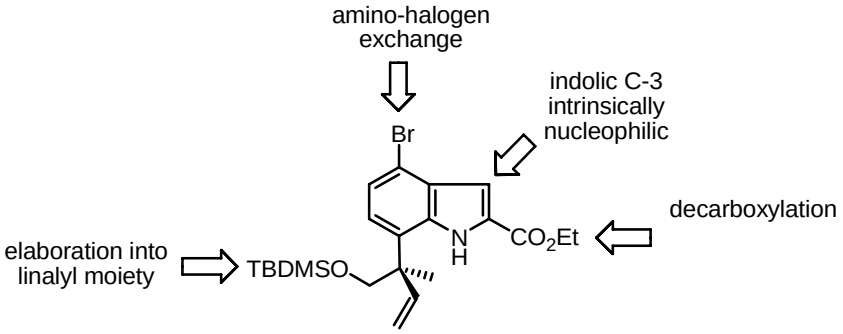
The latter is presumably formed *via* a nitrene insertion into the C-H bond of one of the methyl groups of the solvent. In addition to the concerted pathway involving the singlet nitrene, the enamide (**3.81**) may also arise from a radical-type process involving the corresponding triplet nitrene.




**Scheme 3.29** Conversion of TBDMS ether (**3.73**) into indole (**3.78**).

In summary, indole (**3.78**), an advanced intermediate in a planned enantioselective total synthesis of lyngbyatoxin A, was prepared in 9 steps and with >95% *ee* from readily available allylic alcohol (**3.22**). The key features of this route are: i) a Sharpless-Katsuki asymmetric epoxidation of (**3.22**) for initial introduction of chirality, ii) complete enantiospecific Jung rearrangement of chiral vinyl epoxide (**3.36**) to install the all-carbon quaternary centre of the target molecule, iii) formylation of (**3.38**) *via* chemo-and regioselective iodine-lithium exchange and iv) clean formation of the indole nucleus through the Hemetsberger-Knittel reaction.

It is noted that indole (**3.78**) is conveniently functionalized so as to allow its conversion into lyngbyatoxin A: the C-3 indolic position is intrinsically nucleophilic, whereas the bromine at C-4 provides a suitable handle for insertion of the required amino functionality; the TBDMS-protected alcohol should allow the construction of the linalyl appendage by simple functional group manipulation (Figure 3.3).




**3.78**

**Figure 3.3**

# CHAPTER 4
# Synthetic Strategy Towards the Teleocidins B

## 4.1 - Installation of the All-Carbon Quaternary Stereocenters

The teleocidins B (**1.3**) to (**1.6**), which possess two all-carbon quaternary stereocentres[4.1] embedded within a 6-membered carbocyclic framework, present a significantly greater synthetic challenge than the previously discussed lyngbyatoxin A (**1.1**).

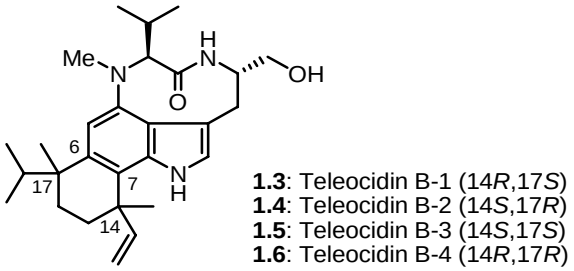



**Figure 4.1** Structure of the teleocidins B.

The benzylic tetrasubstituted carbon at C-17 was envisioned to be stereoselectively installed during the formation of the C-6–C-17 bond, which was to take place *via* an intramolecular asymmetric Heck reaction (IAHR).[4.2]

The (Mizoroki)-Heck reaction[4.3] refers to the palladium-catalyzed arylation or vinylation of olefins. Its intramolecular asymmetric variation is currently one of the most reliable methods for the enantioselective construction of congested quaternary stereogenic centres.[4.1,4.2,4.4] In the IAHR, higher asymmetric induction is typically

[4.1] For reviews on the synthesis of quaternary carbon centres see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591. (c) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Christoffers, J.; Baro, A. in "Quaternary Stereocenters, Challenges and Solutions for Organic Synthesis" **2005**, Wiley-VCH, New York. (d) Barriault, L.; Denissova, I. *Tetrahedron* **2003**, *42*, 1688.

[4.2] For selected reviews on the IAHR see: (a) De Meijere, A.; Bräse, S. in "Handbook of Organopalladium Chemistry for Organic Synthesis" (Negishi, E., ed.) **2002**, 1223, John Wiley & Sons. (b) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1. (c) Link, J. T. *Organic Reactions* **2002**, *60*, 157.

[4.3] (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, Jr., J. P. *J. Org. Chem.* **1972**, *37*, 2320.

[4.4] For selected examples where the IAHR was use in the construction of tetrasubstituted carbon centers within total synthesis see: (a) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959. (b) McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 6094. (c) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423. (d) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028. (e) Trost, B. M.; Tasker, A. S.; Rüther, A.; Brandes, A. *J. Am. Chem.*

obtained when the so-called cationic mechanism operates.[4.5] This cationic pathway is usually invoked when discussing the IAHR of unsaturated triflates[4.6] in the presence of a bidentate chiral ligand. Importantly, under these conditions, the chiral ligand is believed to remain fully chelated to palladium in all the steps of the catalytic cycle[4.7] thus ensuring a high chiral induction.

These points are nicely illustrated in the preparation of the pentacycle (**4.2**), an advanced intermediate in the total synthesis of (+)-xestoquinone (**4.3**), reported by

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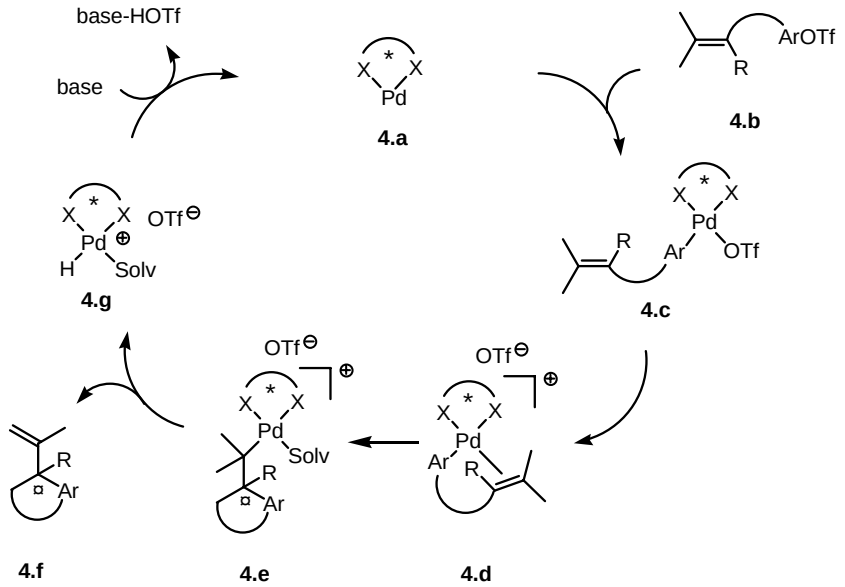
*Soc.* **1991**, *113*, 670. (f) Kojima, A.; Takemoto, T.; Sodeoka, M.; Shibasaki, M. *J. Org, Chem.* **1996**, *61*, 4876. (g) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477.

[4.5] For a notorious example in the IAHR were the so-called neutral pathway proceeds with higher enantioselectivity than the corresponding cationic, see: Overman, L. E.; Poon, D. J. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 518.

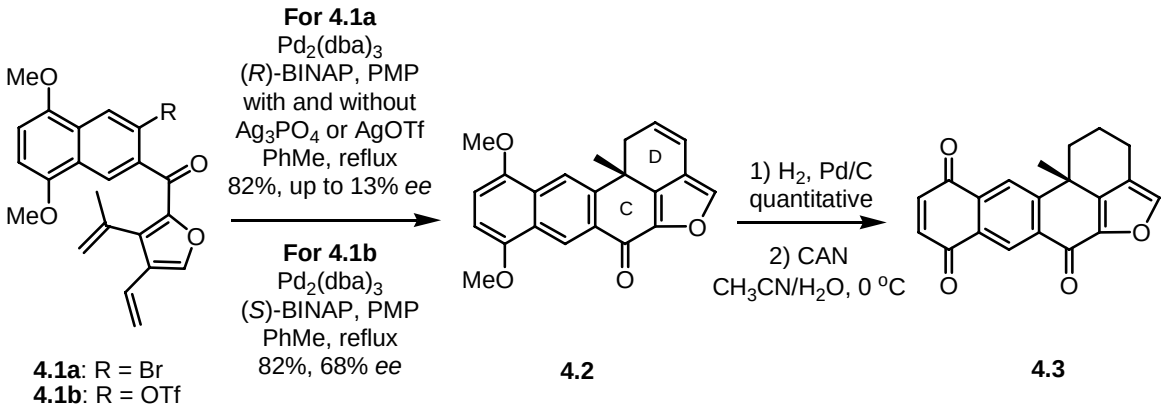
[4.6] Addition of halogen scavengers (*e.g.*, Ag(I) and Tl(I)) to the reaction mixture often allows the use of aryl and vinyl halides in the IAHR. See refs. 4.2.

[4.7] The catalytic cycle for the cationic IAHR is shown in Scheme 4A (see also refs. 4.2). Oxidative addition of aryl triflate (**4.b**) to the Pd(0) species (**4.a**), bearing a chiral bidentate ligand, affords the Pd(II) intermediate (**4.c**). The latter undergoes triflate dissociation, thus liberating a coordination site at palladium. This allows the alkene to complex onto the metal to form the cationic intermediate (**4.d**) which undergoes *syn* insertion into the Pd-Ar bond to give the $\sigma$-complex (**4.e**). $\beta$-Hydride elimination then delivers the desired alkene (**4.f**) (the newly formed quaternary carbon centre is marked ☼). Base-promoted reductive elimination of the Pd(II) species (**4.g**) finally regenerates the Pd(0) species (**4.a**).




**Scheme 4.A** Cationic pathway for the IAHR.

Keay and co-workers.[4.8] The benzylic quaternary carbon center together with the C and D rings of (**4.2**) were created *via* two tandem intramolecular Heck reactions. When naphthyl bromide (**4.1a**) was used, either under neutral or cationic conditions, poor enantiomeric excesses (5-13% *ee*) were obtained. On the other hand, the use of triflate (**4.1b**) dramatically improved the cyclization process, yielding the pentacycle (**4.2**) in 82% yield and with good enantiomeric excess (68% *ee*).




**Scheme 4.1** Synthesis of (+)-xestoquinone (**4.3**) *via* a cascade IAHR as the key step.

In view of this, aryl triflate (**4.4**) was thought to be a suitable precursor to stereoselectively access the quaternary carbon at C-17 in the teleocidins B. Concerning the regioselectivity in the cyclization step we expected that, in accordance with the Balwin rules for ring-closing reactions[4.9] and in line with what is usually observed in metal-catalyzed cross coupling reactions,[4.10] the desired 6-*exo*-*trig* cyclization to C-17 would be favoured over the alternative 5-*endo*-*trig* to C-14. The presence of a chiral bisphospine ligand in the reaction would hopefully provide an efficient discrimination between the *Re* and the *Si* faces of the tetrasubstituted double bond (as in intermediate (**4.5**)). It is noted that due to the two freely rotating methyl groups in the $\sigma$-complex (**4.6**), $\beta$-hydride elimination was anticipated to proceed faster than the policyclization cascade process[4.11] involving the vinylic double bond at C-14.

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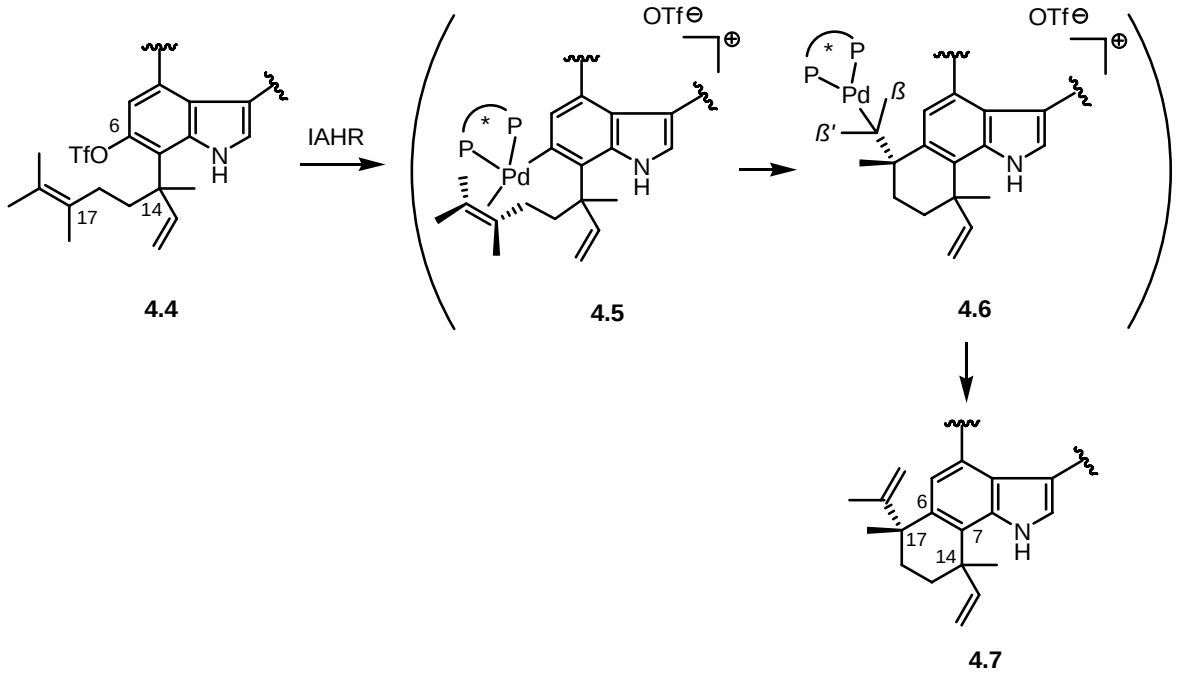
[4.8] (a) Maddford, S. P.; Andersen, W. A. Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766. For an alternative total synthesis of (+)-xestoquinone (**4.3**) also based on an IAHR see: (b) Miyazaki, F.; Uotsu, K.; Shibasaki, M. *Tetrahedron* **1998**, *54*, 13073.

[4.9] (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

[4.10] Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003. See also refs. 4.2.

[4.11] For selected examples of Heck-type polyene cyclization see: (a) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813. (b) Burns, B.; Grigg, R.;




**Scheme 4.2** Planned construction of the carbocyclic framework and the all-carbon quaternary stereocenter at C-17 of the teleocidins B using an IAHR.

On the other hand, the C-14 quaternary carbon in the teleocidins B was planned to be installed *via* a regioselective aromatic Claisen rearrangement[4.12,4.13] of a suitable 6-allyoxyindole.

Moody and co-workers already showed that the Claisen rearrangement of 6-allyoxyindoles is completely regioselective to the 7-position of the indole nucleus.[4.14] These authors reported that the Claisen rearrangement of (**4.8**) occurred readily in

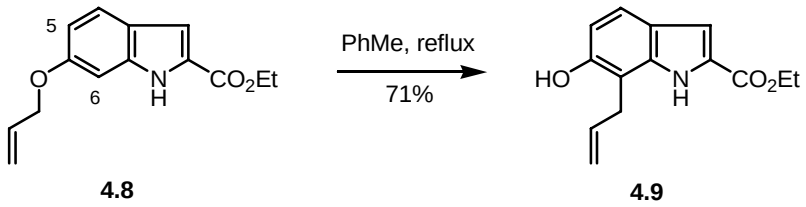
Santhakumar, V.; Sridharan, V.; Steveson, P.; Worukun, T. *Tetrahedron* **1992**, *48*, 7297. (c) Carpenter, N. E.; Kucera, D. J. Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846. (d) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421. (e) Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304.

[4.12] For selected reviews on the Claisen rearrangement see: (a) Bennett, G. B. *Synthesis* **1977**, 589. (b) Lutz, R. P. *Chemical Reviews* **1984**, *84*, 205. (c) Ito, H.; Taguchi, T.; *Chem. Soc. Rev.* **1999**, *28*, 43.

[13] For (rare) examples of enantioselective aromatic Claisen rearrangement see: (a) Ito, H.; Taguchi, T. *Tetrahedron Letts*. **1997**, *38*, 4815. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815.

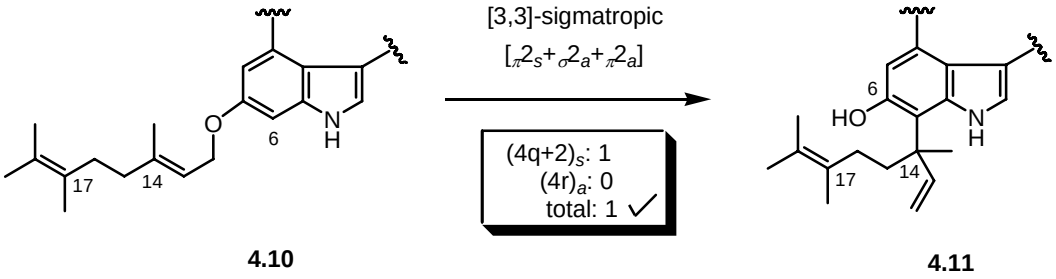
[4.14] For examples of applications in synthesis of the 6-allyloxyindole→7-ally-6-hydroxyindole Claisen rearrangement see: (a) Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1129. (b) Martin, T.; Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1391. (c) Martin, T.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 241.

refluxing toluene to give 7-allyl-6-hydroxyindole (**4.9**) with no evidence for products from the alternative rearrangement to C-5.[4.14a]




**Scheme 4.3** Preparation of 7-allyl-6-hydroxyindole (**4.9**) *via* a regioselective Claisen rearrangement of 6-allyloxyindole (**4.8**).

Thus, indole ether (**4.10**) was envisioned to be a convenient precursor to the desired 6-hydroxyindole (**4.11**). Regarding the double bond regioselectivity, it was anticipated that, due to the pericyclic nature of the Claisen rearrangement, only the trisubstituted double bond at C-14 would be involved in this process.



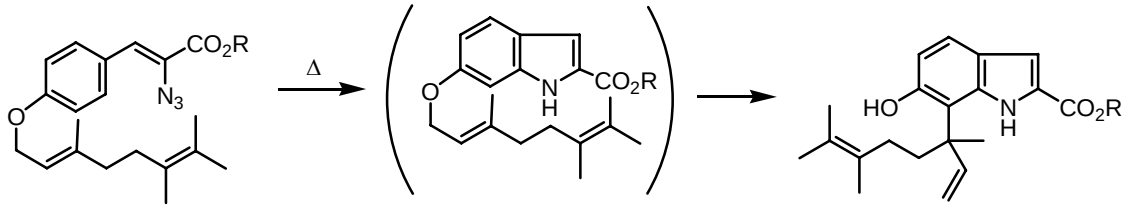

**Scheme 4.4** Planned construction of the all-carbon quaternary stereocenter at C-14 of the teleocidins B using regioselective Claisen rearrangement.

## 4.2 - Construction of the Indole Ring

The indole nucleus of the teleocidins B was planned to be accessed using the previously discussed Hemetsberger-Knittel reaction.[4.15] The reader is referred to Chapter 2, Section 2.2 of the present thesis for further details.

[4.15] (a) Hemetsberger, H.; Knittel, D.; Weidmann, H. *Monatsh. Chem.* **1969**, *100*, 1599-1603. (b) Hemetsberger, H.; Knittel, D.; Weidmann, H. *Monatsh. Chem.* **1970**, *101*, 161-165. (c) Hemetsberger, H.; Knittel, D. *Monatsh. Chem.* **1972**, *103*, 194-204. (d) Murakami, Y.; Watanabe, T.; Suzuki, H.; Kotake, N.; Takahashi, T.; Toyonari, K.; Ohno, M.; Takase, K.; Suzuki, T.; Kondo, K. *Chem. Pharm. Bull.* **1997**, *45*, 1739.

It is noted that since the Hemetsberger-Knittel reaction and the aromatic Claisen rearrangement are to take place under purely thermal conditions, it is possible to envision that the 6-hydroxyindole (**4.14**) could be obtained from azidocinnamate (**4.12**) in one pot *via* a tandem process (Scheme 4.5).




**4.12**, R = Me or Et **4.13**, R = Me or Et **4.14**, R = Me or Et

**Scheme 4.5** (Potential) tandem Hemetsberger-Knittel/aromatic Claisen rearrangement.

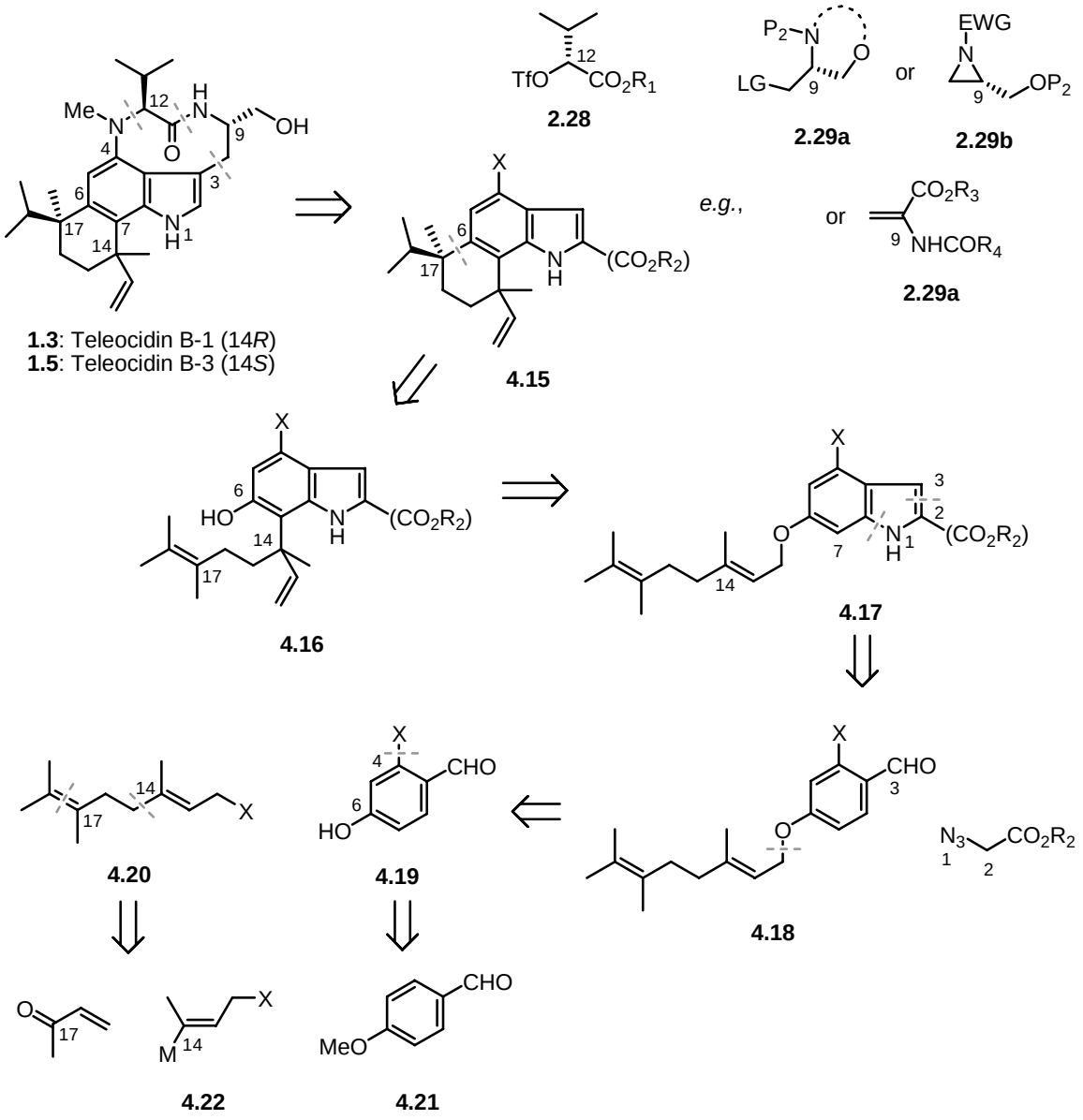
## 4.3 - Retrosynthetic Analysis of Teleocidins B

The retrosynthetic guidelines for the teleocidins B, exemplified for teleocidins B-1 and B-3, are shown in Scheme 4.6. The key steps considered are an IAHR and a regioselective Claisen rearrangement for accessing the two quaternary carbons at C-17 and C-14, respectively, and the Hemetsberger-Knittel reaction for the construction of the indole nucleus.

Regarding the construction of the 9-membered lactam ring as well as the installation of the amino-alcohol moiety at the C-3 indolic position, these were planned to be accessed in the same manner as previously described for lyngbyatoxin A (**1.1**) (*vide* Chapter 2, section 2.3).

The key indole intermediate (**4.15**) was envisioned to arrive *via* the IAHR[4.2] of the triflate of (racemic) 6-hydroxyindole (**4.16**). The latter could in turn be obtained by means of a regioselective Claisen rearrangement[4.12] of indole ether (**4.17**).

Indole (**4.17**) was planned to be assembled *via* the Hemetsberger-Knittel reaction[4.15] of the vinyl azide obtained by condensation of benzaldehyde (**4.18**) with an azidoacetate.




**Scheme 4.6** Retrosynthetic guidelines for teleocidins B.

The aryl ether (**4.18**) would arrive *via* a Williamson ether synthesis[4.16] type reaction or, alternatively, by means of a Mitsunobu reaction[4.17] of phenol (**4.19**) and allylic

[4.16] (a) Williamson, W. *J. Chem. Soc.* **1852**, *106*, 229. For reviews see: (b) Hill, M.; Dronsfield, A. *Educ. Chem.* **2002**, *39*, 47. (c) Feuer, H.; Hooz, J. in "The Chemistry of Functional Groups" (Patai, S., ed.) 1967, 445, Wiley, New York.

[4.17] (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380. (b) Mitsunobu, O.; Yamada, M.; Mukayaima, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935. For selected reviews see (c) Mitsunobu, O.

halide/alcohol (**4.20**). Phenol (**4.19**) should be readily available from *para*-anisaldehyde *via* DoM methodology.[4.18] The allylic substrate (**4.20**) could be obtained by a Michael addition[4.19] of (**4.22**) to methyl vinyl ketone followed by a Wittig-type reaction.[4.20]

*Synthesis* **1981**, 1. (d) Hughes D. L. *Org. React.* **1992**, *42*, 335. (d) Lawrence S. *PharmaChem* **2002**, *1*, 12.

[4.18] For general reviews on DoM see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Narashimahn, N. S.; Mali, R. S. *Synthesis* **1983**, 957.

[4.19] Michael, A. *J. Prakt. Chem./Chem.-Ztg.* **1887**, *35*, 349. For selected reviews see: (b) Hunt, D. A. *Org. Prep. Proced. Int.* **1989**, *21*, 705. (b) Kozlowski, J. A. in "Comprehensive Organic Synthesis". (Trost, B. M., Fleming, I., ed.) **1991**, *4*, 169, Pergamon, New York.

[4.20] (a) Wittig, G.; Schölkopf, U. Ber. Dtsch. Chem. Ges. 1954, 87, 1318. For reviews see: (b) Murphy, P.J.; Brennan, J. *Chem. Soc. Rev.* **1988**, *17*, 1. (c) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1. (d) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. (e) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *62*, 1733. For a review see (f) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1988**, *89*, 863.

# CHAPTER 5
# Synthetic Studies Towards the Teleocidins B
# Results and Discussion

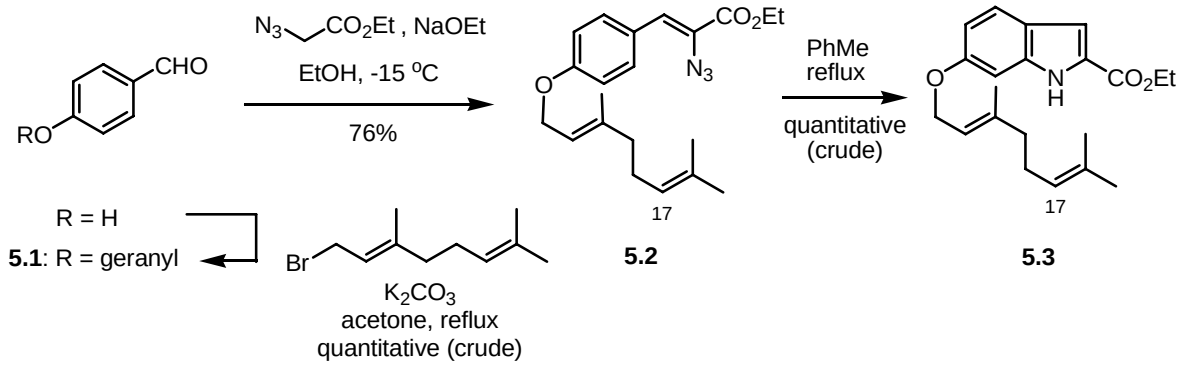
## 5.1 - Studies Towards the Teleocidins B's Carbocyclic Framework

To test the feasibility of the discussed approach towards the teleocidins B (*vide* Chapter 4), and in particular to investigate the construction of the carbocyclic framework in this family of compounds, we began by performing various model studies.

### 5.1.1 - Installation of the C-14 All-Carbon Quaternary Stereocenter

We started by investigating the construction of the tetrasubstituted carbon at C-14. To this end we turned our attention to a simplified model compound, 6-allyloxyindole (**5.3**), which lacks a methyl group at C-17 (indole numbering).

Following a literature procedure,[5.1] *para*-hydroxybenzaldehyde was etherified with geranyl bromide in the presence of $K_2CO_3$ in refluxing acetone, affording aryl ether (**5.1**) quantitatively and with high purity (Scheme 5.1). The latter was subjected to the reaction with excess of ethyl azidoacetate in the presence of freshly prepared ethanolic NaOEt at low temperature to produce vinyl azide (**5.2**) in good yield (76%). The Hemetsberger-Knittel reaction of azidocinnamate (**5.2**) was then accomplished in refluxing toluene delivering the known indole (**5.3**) in excellent yield and high purity.[5.2]

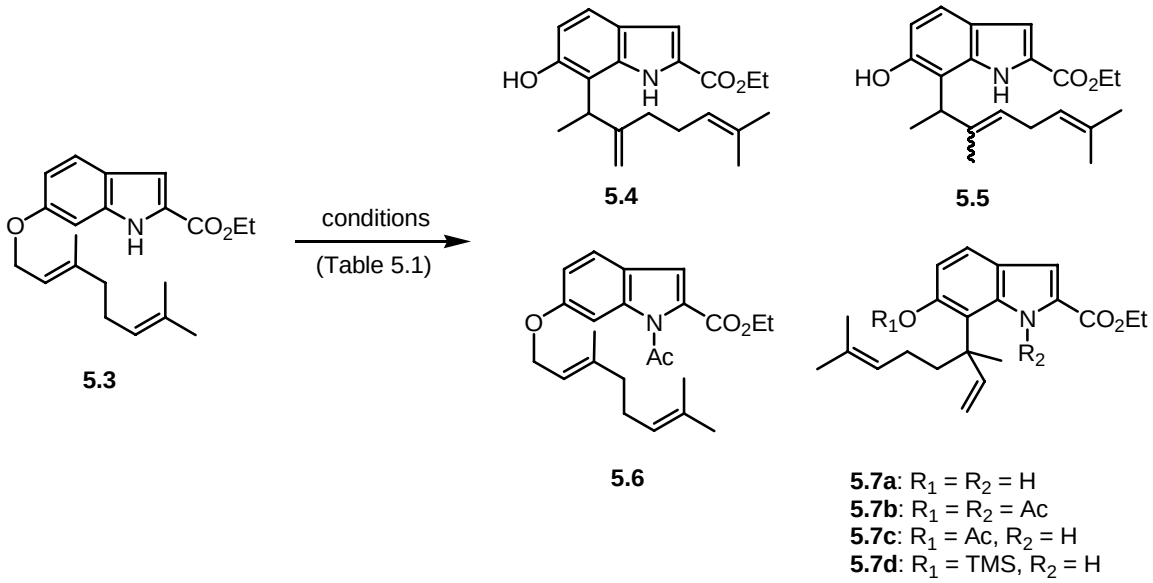



**Scheme 5.1** Preparation of indole ether (**5.3**) *via* the Hemetsberger-Knittel reaction.

[5.1] Shinmon, N.; Cava, M. *J. Chem. Soc., Chem. Commun.* **1980**, 1020.
[5.2] Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1129.

We next attended to the installation of the C-14 quaternary carbon, which was to take place *via* an aromatic Claisen rearrangement of (**5.3**).[5.3,5.4] Not entirely unexpectedly this step proved not to be straightforward. The different reaction conditions tested and the respective product distribution obtained are shown in Table 5.1.

**Table 5.1** Aromatic Claisen rearrangement of 6-oxyallylindole (**5.3**).

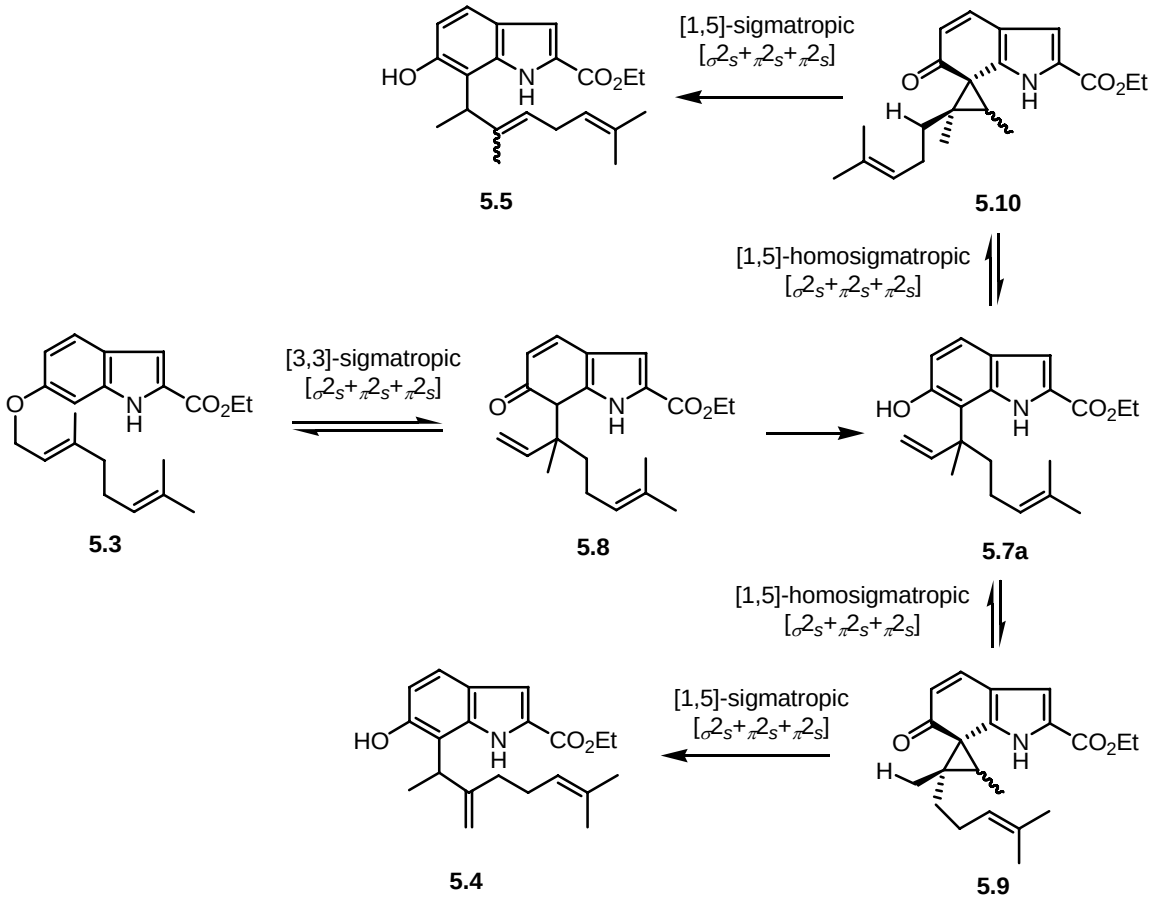



| Entry | Reaction Conditions[a] | Product Distribution[b] |
|---|---|---|
| 1 | *N*,*N*-dimethylaniline | 55% of (**5.4**) and (**5.5**) as a (1:1) inseparable mixture |
| 2 | NaOAc (1.5 eq.) in $Ac_2O$ at 170 °C | 45% of (**5.6**), 33% of (**5.7c**), 5% of (**5.3**) |
| 3 | $Ac_2O$ in *N*,*N*-dimethylaniline (1:1, v:v) | <5% of (**5.6**), 61% of (**5.7b**) |
| 4 | i) HMDS (10 eq.) in *N*,*N*-dimethylaniline ii) HCl/EtOH (0 °C) | 88% of (**5.7a**) |

[a] All reactions performed at 195 °C in a sealed tube;
[b] Isolated yields.

[5.3] For selected reviews on the Claisen rearrangement see: (a) Bennett, G. B. *Synthesis* **1977**, 589. (b) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. (c) Ito, H.; Taguchi, T.; *Chem. Soc. Rev.* **1999**, *28*, 43.
[5.4] For (rare) examples of enantioselective aromatic Claisen rearrangement see: (a) Ito, H.; Taguchi, T. *Tetrahedron Lett*. **1997**, *38*, 4815. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815.

When 6-allyoxoindole (**5.3**) was subjected to the usual conditions for the aromatic Claisen rearrangement (*i.e.*, refluxing in dimethylaniline), only an equimolar inseparable mixture of (**5.4**) and (**5.5**) was obtained (entry 1, Table 5.1). These products presumably arrive *via* the so-called abnormal Claisen rearrangement.[5.5] The abnormal Claisen rearrangement consists of a sequence of back-to-back symmetry allowed sigmatropic rearrangements[5.6] by which the normal Claisen product (*e.g.*, (**5.7a**)) is converted into the thermodynamic more favourable, abnormal products (*e.g.*, (**5.4**) and (**5.5**)) *via* a spiro intermediate (*e.g.*, (**5.9**) and (**5.10**)) (Scheme 5.2).




**Scheme 5.2** (Proposed) formation of 6-hydroxyindoles (**5.4**) and (**5.5**) *via* the abnormal Claisen rearrangement.

[5.5] (a) Scheinmann, F.; Barner, R.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1603. (b) Hansen, H.-J. in "Mechanisms of Molecular Migrations" (Thyagarajan, B. S., ed.) **1971**, *3*, 177, Wiley-Interscience, New York.

[5.6] (a) R. B. Woodward and R. Hoffman in "The Conservation of Orbital Symmetry" **1970**, Verlag Chemie, Academid Press, New York. (b) Ian Fleming in "Pericyclic Reactions" **1999**, *67*, Oxford Science Publications, Oxford Chemistry Primers.

The abnormal Claisen rearrangement can in principle be blocked by trapping the desired Claisen product, 6-hydroxyindole (**5.7a**), before it undergoes the subsequent [1,5]-hydrogen shift.[5.7] Traditionally this has been accomplished by *in situ* conversion into the corresponding acetate, indole (**5.7c**).[5.7] When the conditions developed by Kishi (*i.e.*, NaOAc in refluxing $Ac_2O$)[5.7a] were used, we hoped to obtain the rearranged indole as the corresponding *N*,*O*-diacetate (**5.7b**). The desired rearranged product was indeed formed, but as the *O*-acetate (**5.7c**) and in only in low yield (33%). The main product was instead the *N*-acylated compound (**5.6**), which was isolated in 45% (entry 2, Table 5.1). This result implied that the *N*-acylated indole (**5.6**) does not undergoes the desired Claisen rearrangement, presumably due to steric reasons. Performing the reaction in a refluxing mixture of $Ac_2O$ and dimethylaniline inverted the previous ratio, delivering the known indole (**5.7c**) as the main product (61% yield) as well as a small amount of the *N*-acylated by-product (**5.6**) (<5% yield) (entry 3, Table 5.1).[5.8] The highest selectivity for the desired rearranged product was obtained using the conditions developed by Fukuyama (*i.e.*, reflux in a mixture of HMDS and dimethyaniline)[5.7c] thus trapping (**5.7a**) as the corresponding TMS ether (**5.7d**). Subsequent *in situ* acidic hydrolysis yielded (**5.7a**) in high yield (88%) over the two steps (entry 4, Table 5.1).

As expected the Claisen rearrangement of 6-allyloxyindole (**5.3**) was completely regioselective for the 7-position of the indole nucleus.[5.9] In order to rationalize this result the relative energies of (**5.16**) and (**5.17**), simplified versions of the two possible intermediates in this process, corresponding to the Claisen rearrangements to the C-7 and C-5 positions, respectively, were calculated.[5.10] In accordance with the Bell-Evans-Polanyi principle, the relative energies of high-energy intermediates such as (**5.16**) and (**5.17**) should correlate well with the relative barriers for the two possible rearrangements (**5.14**) and (**5.15**), respectively.[5.11]

---

[5.7] (a) Karanewsky, D. S.; Kishi, Y. *J. Org. Chem.* **1976**, *41*, 3026. (b) Falling, S. N.; Rapoport, H. *J. Org. Chem.* **1980**, 45, 1260. (c) Fukuyama, T.; Tangquing, L.; Peng, G. *Tetrahedron Lett.* **1994**, *35*, 2145.

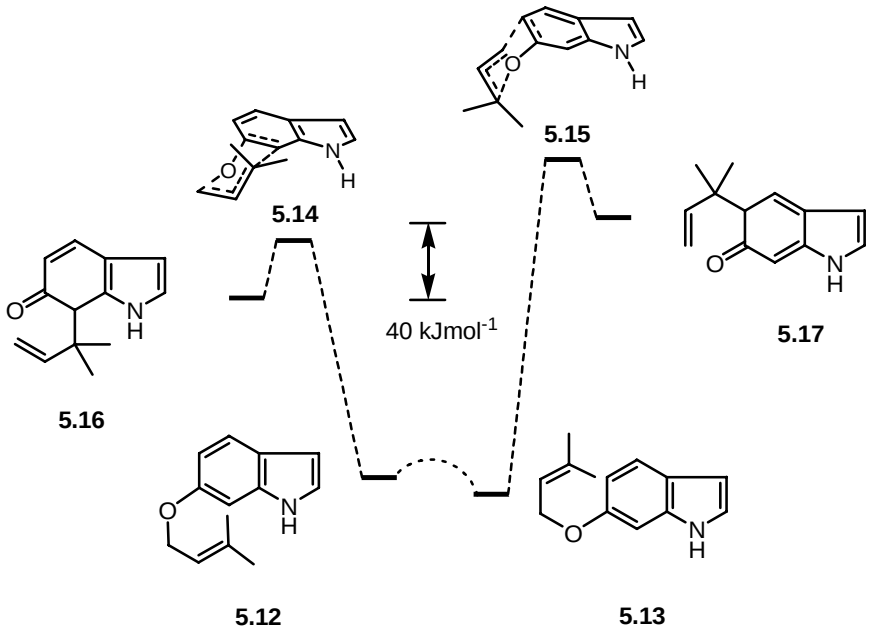
[5.8] The acetylated indole (**5.7c**) has previously been used in synthetic studies towards lyngbyatoxin A, see: Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1129.

[5.9] For examples of applications in synthesis of the 6-allyloxyindole→7-ally-6-hydroxyindole Claisen rearrangement see: (a) Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1983**, 1129. (b) Martin, T.; Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1391. (c) Martin, T.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 241.

[5.10] The calculations were performed by Associate Professor Per-Ola Norrby.

[5.11] For a discussion see: Jensen, F. in "Introduction to Computational Chemistry", 1999, Wiley, Chichester.

The structures were optimized at the B3LYP/6-31G* level of theory and the conformations where chosen to represent the immediate product from a chair transition state. A difference of 40 kJmol$^{-1}$ in favour of (**5.16**) was found, in good agreement with the observed selectivity.[5.12,5.13] The reason for the high energy difference between superficially similar intermediates was ascribed to the fact that that only the latter intermediate preserves an aromatic pyrrole moiety in its structure (Scheme 5.3).




**Scheme 5.3** B3LYP/6-31G* potential energy surface diagrams for the competitive aromatic Claisen rearrangement of model compound (**5.11**).

[5.12] Gozzo, F. C.; Fernandes, S. A.; Rodrigues, D. C.; Eberlin, M. N.; Marsaiolo, A. J. *J. Org. Chem.* **2003**, *68*, 5493.

[5.13] The relative ground states energies of the conformers leading to the two high energy intermediates can also be an important factor in determining the regioselectivity in the aromatic Claisen rearrangement (see ref. 5.11). However, for the case in study, the energy difference between the two hypothetical transition states (**5.14**) and (**5.15**) is expected to be much larger than the energy difference between the two ground states conformers (**5.12**) and (**5.13**).

## 5.1.2 – Studies Towards the Construction of Teleocidins B's Carbocyclic Framework

Having installed the C-14 quaternary carbon we then focused on the key intramolecular (asymmetric) Heck reaction (IAHR) which would result in the construction of the carbocyclic framework. In particular we wished to investigate how the severe steric bulk, derived from the newly installed neighbouring quaternary carbon at C-14, would affect this transformation.

The required triflate (**5.7e**) for the IHR was prepared in good yield (75%) by treating (**5.7a**) with $Tf_2O$ in the presence of pyridine at low temperature. With triflate (**5.7e**) in hand, we then addressed the cyclization reaction. The different conditions tested are presented in Table 5.2.

For the cyclization of (**5.7e**) we started by investigating the use of *rac*-BINAP (entry 1, Table 2). To our surprise, the product obtained was not the expected cyclohexadieno-indole (**5.19**). Instead, NMR analysis showed the cyclopentadieno-indole (**5.18**), presumably formed *via* what is normally considered to be a disfavoured 5-*endo*-*trig* cyclization mode.

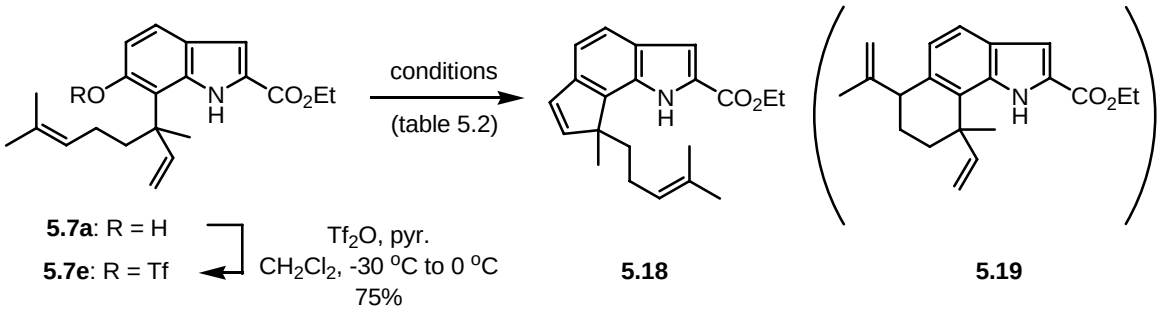
In order to obtain a better understanding of this process and, in particular to see if the regioselectivity of the cyclization could be reversed into the desired 6-*exo* mode, we went on to screen several readily available ligands.

We started by investigating the use of the classic $PPh_3$ (with and without LiCl as additive, entries 2 and 3 and in the form of $Pd(PPh_3)_4$, entry 4, Table 5.2, respectively), $AsPPh_3$ (entry 5, Table 5.2) and then moved on to bulkier ligands such as $P^tBu_3$ (entry 6, Table 5.2) and Buchwald's biphenyl dicyclohexyl phosphine (entry 7, Table 5.2). However, all of these monodentate ligands failed to deliver product and only starting material was recovered. This suggests that for this system, and in line with the generally accepted mechanism for the cationic pathway in the Heck reaction, a bidentate ligand is required for the stability of the active catalyst.

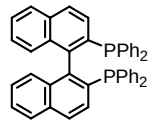
Hence we subsequently investigated bidentate ligands other than *rac*-BINAP. In contrast to the monodentate ligands, all the bidentate phosphines screened succeeded in promoting the cyclization reaction, but again only the 5-*endo* product (**5.18**) was obtained (entries 8 to 13, Table 5.2). The incomplete conversion, even after long reaction times, observed when dppbz and triphos were used (entries 12 and 13, Table

5.2, respectively) together with the fact that a slightly faster reaction was observed for dppe and dppp (entries 10 and 11, Table 5.2, respectively) suggests that ideally the ligand bite angle should be slightly less than 90°.

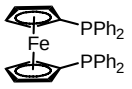
**Table 5.2** Intramolecular Heck reaction of triflate (**5.7e**).



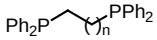

| Entry | Conditions[a] | Outcome[b] |
|---|---|---|
| 1 | $Pd(OAc)_2$, *rac*-BINAP, 3½ h | 88% of **5.18** |
| 2 | $Pd(OAc)_2$, $PPh_3$, $NEt_3$, 28 h | only **5.7e** |
| 3 | $Pd(OAc)_2$, $PPh_3$, $NEt_3$, LiCl, 28 h | only **5.7e** |
| 4 | $Pd(PPh_3)_4$, LiCl, $NEt_3$, 28h | only **5.7e** |
| 5 | $Pd_2(dba)_3$, $AsPh_3$, 30 h | mainly **5.7e**<br>traces of **5.18** |
| 6 | $Pd(OAc)_2$, $P^tBu_3$, 30 h | mainly **5.7e**<br>traces of **5.18** |
| 7 | $Pd(OAc)_2$, biphenyl dicyclohexyl phosphine, 43 h | mainly **5.7e**<br>traces of **5.18** |
| 8 | $Pd(OAc)_2$, dppf, 3½ h | 88% of **5.18** |
| 9 | $Pd(OAc)_2$, dppb, 3½ h | 85% of **5.18** |
| 10 | $Pd(OAc)_2$, dppp, 3½ h | 88% of **5.18** |
| 11 | $Pd(OAc)_2$, dppe, 3½ h | 94% of **5.18** |
| 12 | $Pd(OAc)_2$, dppbz, 24 h | 2.6:1, **5.18**:**5.7e**[c] |
| 13 | $Pd(OAc)_2$, triphos, 24 h | 1:1.8, **5.18**:**5.7e**[c] |



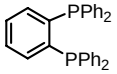
*rac*-BINAP



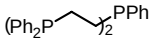
dppf



dppe, n = 1
dppp, n = 2
dppb, n = 3



dppbz



triphos

[a] All reactions were performed in refluxing THF and, unless stated otherwise, $K_2CO_3$ was used as the base;
[b] Isolated yields;
[c] Ratio based on crude $^1$H-NMR.

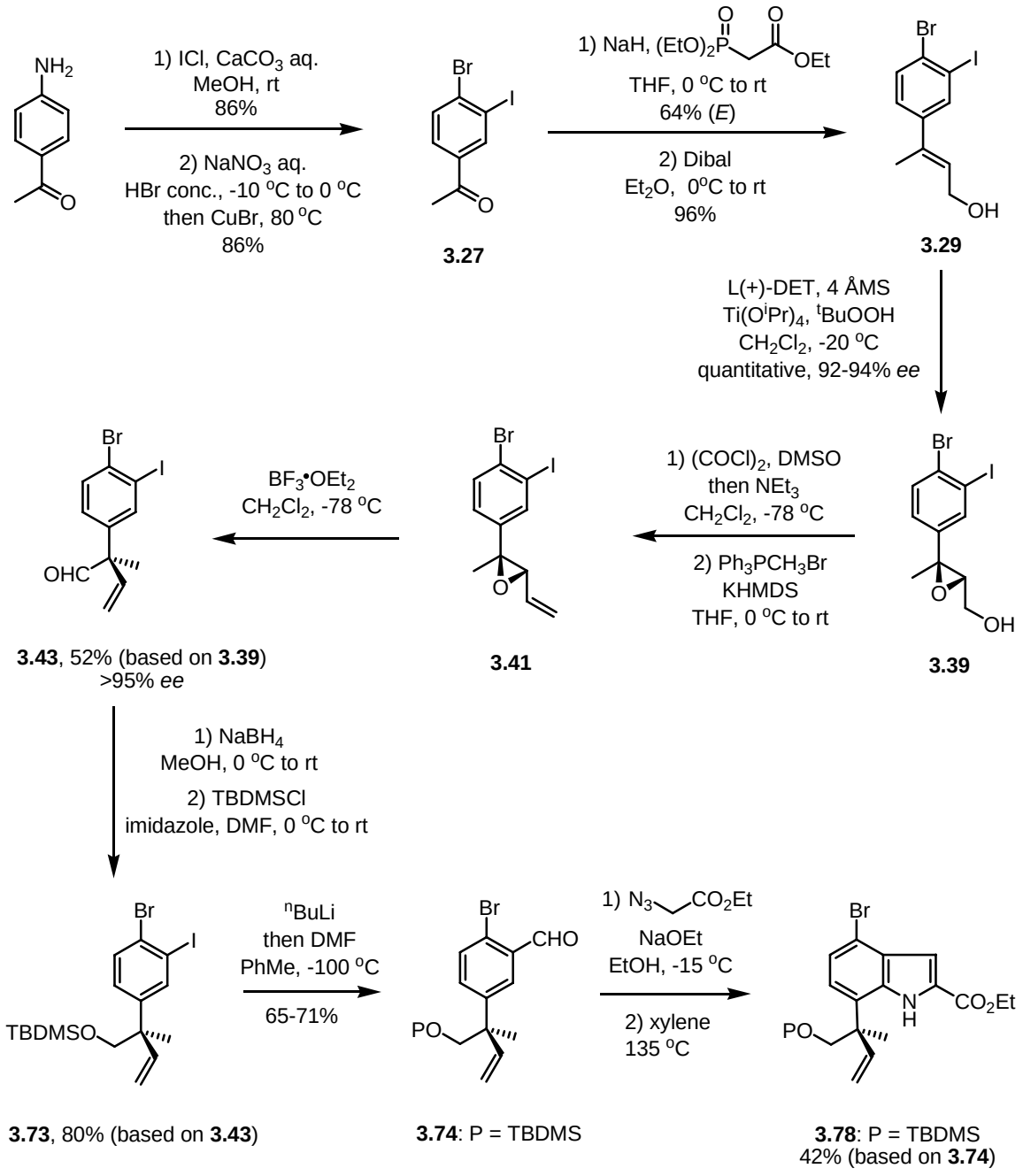
Whereas 5-*endo* type products in intramolecular Heck reactions are not unprecedented they are rare, being confined to special substrates such as *N*-vinyl-2-haloarylamines,[5.14] aryl/alkenyl halides containing an appropriate α, β-unsaturated carbonyl group[5.15] or 1,1-difluoro-1-alkenes.[5.16] Furthermore, their formation can frequently be rationalized by alternative mechanisms other than a direct 5-*endo* cyclization.[5.17] Additionally, when this cyclization mode operates it typically requires harsher conditions and often produces only low yields of the products,[5.18] whereas in our case indole (**5.18**) was obtained in high yield and the reaction was complete in about 3½ h.

To the best of our knowledge, this is the first example where, having available the possibility for a 6-*exo-trig* path, the IHR occurs exclusively to afford high yields (up to 94%) of the 5-*endo-trig* cyclized product. This result is likely to be a consequence of two factors: i) the steric bulk of the neighboring quaternary carbon which positions and eventually locks the vinylic double bond of (**5.7e)** in the proximity of the oxidatively-added Pd and ii) in the migratory insertion step, occurring in the coordination sphere of Pd, the bond formation is initiated at a long C-C distance, and can thus occur in geometries that are distinctly different from those allowed in systems for which the Baldwin ring closing rules[5.19] were originally developed.

[5.14] For representative examples see: (a) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *J. Chem. Soc., Chem. Commun.* **2004**, 2824. (b) Watanabe, T.; Arai, S.; Nishida, A. *Synlett* **2004**, 907. (c) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676.
[5.15] O'Connor, B.; Zhang, Y.; Negishi, E. *Tetrahedron Lett.* **1988**, *29*, 3903.
[5.16] Sakoda, K.; Mihara, J.; Ichikawa, J. *J. Chem. Soc., Chem. Commun.* **2005**, 4684.
[5.17] Grigg, R.; Savic, V. *J. Chem. Soc., Chem. Commun.* **2000**, 871.
[5.18] (a) Wiedenau, P.; Monse, B.; Blechert, S.; *Tetrahedron* **1995**, *51*, 1167 (in particular Scheme 7). (b) Gaudin, J.-M. *Tetrahedron Lett.* **1991**, *32*, 6113.
[5.19] (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

# CHAPTER 6
# Concluding Remarks

Indole (**3.78**), a late key intermediate in a projected enantioselective total synthesis of lyngbyatoxin A, was prepared according to Scheme 6.1.

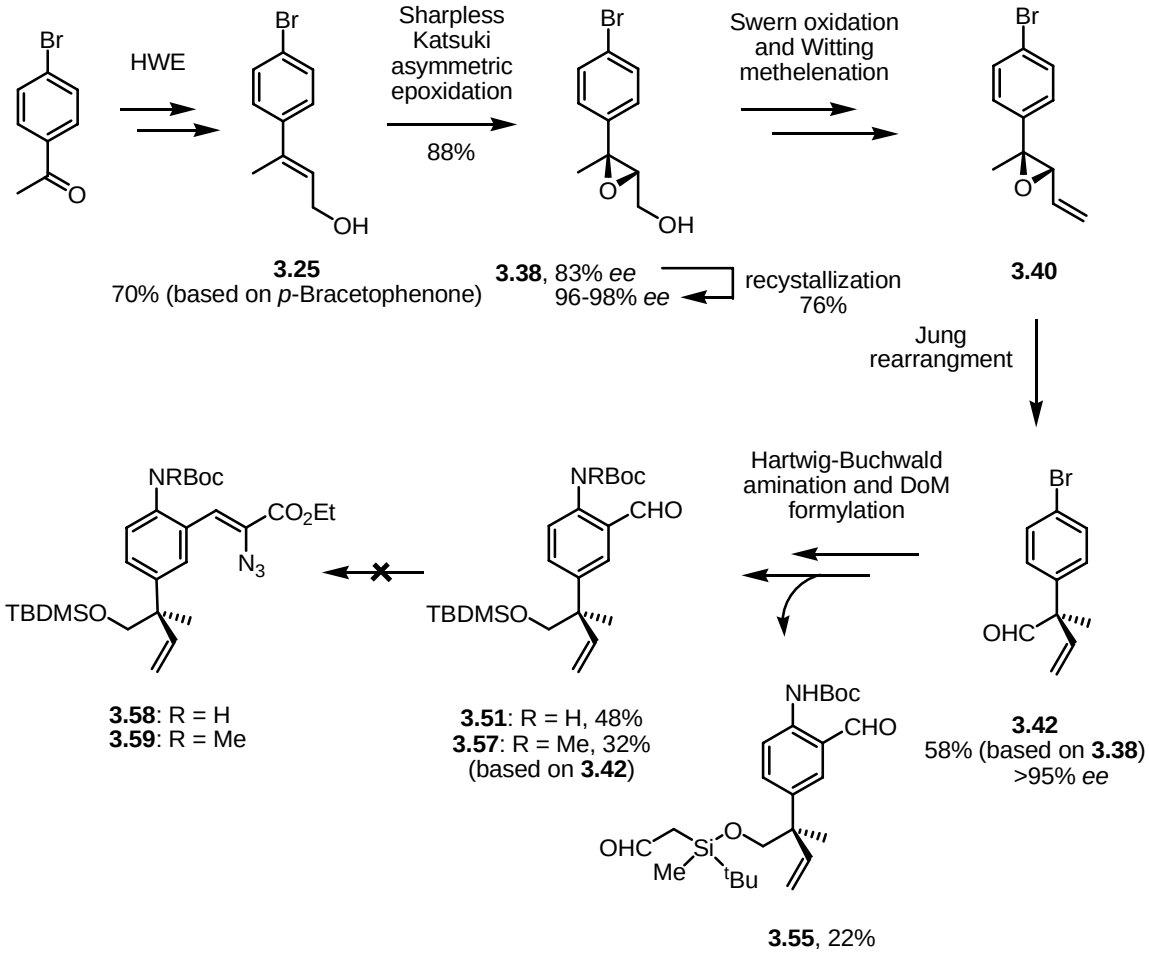



**Scheme 6.1** Preparation of key indole (**3.78**).

*para*-Aminoacetophenone was treated with ICl to afford the corresponding iodinated aniline in high yield (86%). The latter underwent amine-bromine exchange using Sandmeyer conditions delivering di-halogenated acetophenone (**3.27**) in 86% yield. A HWE reaction with the sodium salt of triethylphosphonoacetate afforded, after column chromatography, the corresponding pure *E*-*α*,*β*-unsaturated ester in moderate yield (64%), which was then reduced with Dibal to the allylic alcohol (**3.29**) in 96% yield. Sharpless-Katsuki asymmetric epoxidation produced the epoxy alcohol (**3.39**) quantitatively and with high enantiomeric excess (92-94% *ee*) as a highly crystalline product. The latter was oxidized under Swern conditions to the corresponding epoxy-aldehyde and the crude product obtained was then subjected to Wittig methelenation delivering vinyl-epoxide (**3.41**). After a rapid filtration through a short column of silica gel, the crudely purified vinyl-epoxide (**3.41**) was treated with $BF_3 \cdot Et_2O$ at -78 $^oC$ producing the key quaternary aldehyde (**3.43**) in good yield (52%, based on epoxy-alcohol (**3.39**)) and with complete transfer of chirality (> 95% *ee*), as determined by derivatization using the Alexakis reagent and $^{31}P$-NMR. Reduction of aldehyde (**3.43**) with $NaBH_4$ and conversion of the crude alcohol obtained into the corresponding TBDMS ether (**3.73**) proceeded with good overall yield (80%). After extensive model studies with *ortho*-iodobenzene, we found that formylation at the C-3a position (indole numbering) of silyl ether (**3.73**) could be accomplished *via* a regio- and chemoselective lithium-iodine exchange followed by quenching with DMF if the reaction was carried in toluene at approximately -100 $^oC$. Under these conditions benzaldehyde (**3.74**) was prepared in 65-71% yield. Subsequent NaOEt-promoted condensation with ethylazidoacetate at -15 $^oC$ afforded the corresponding azidocinnamate which, upon heating in xylene, underwent the expected Hemetsberger-Knittel reaction finally furnishing the key indole (**3.78**) in moderate yield (42%, based on (**3.74**)).

In a related approach, benzaldehydes (**3.51**) and (**3.57**), putative intermediates to lyngbyatoxin A, were also prepared (Scheme 6.2). Accordingly, starting from *para*-bromoacetophenone and using a similar sequence of reactions as in Scheme 6.1, the quaternary aldehyde (**3.42**) was obtained in good yield (58%, based on the readily prepared epoxy alcohol (**3.38**)) and with high enantiomeric excess (>95% *ee*). Following functional group manipulation, which included a key high yielding Buchwald-Hartwig amination, *N*-Boc aniline (**3.50**) (not shown) was prepared. After extensive experimentation, the latter was converted into the required benzaldehyde (**3.51**) using DoM methodology. A large excess of $^t$BuLi was necessary for achieving complete conversion in this formylation reaction, the reason being that competitive metallation of the TBDMS protecting group, to afford dialdehyde (**3.55**), was

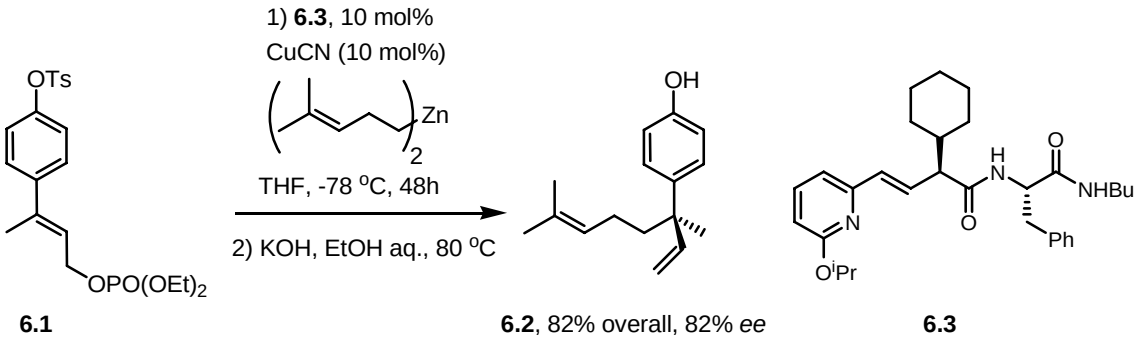
proceeding. Although we never succeeded in converting benzaldehydes (**3.51**) and (**3.57**) into the corresponding vinyl-azides (**3.58**) and (**3.59**), respectively, it is likely that the success of this transformation would be irrelevant. This is because extensive studies in related systems suggested that the presence of a (protected) amino moiety *ortho* to the vinylnitrene functionality is not compatible with the Hemetsberger-Knittel indole synthesis.




**Scheme 6.2** Preparation of benzaldehydes (**3.51**) and (**3.57**).

As is often the case when dealing with asymmetric synthesis, the enantioselective construction of the all-carbon quaternary center in lyngbyatoxin A was the constraining factor in the chosen strategy. While this work was in progress an interesting alternative approach for the catalytic enantioselective installation of benzylic quaternary carbons has been reported. Accordingly, the Hoveyda group disclosed that aromatic allylic phosphates undergo efficient enantioselective Cu-

catalyzed allylic alkylations in the presence of chiral amino acid-based ligands.[6.1,6.2] As a pertinent application of this methodology, a very efficient total synthesis of (-)-sporochnol (**6.2**) from the readily accessible allylic phosphate (**6.1**) was accomplished (Scheme 6.3). This type of reactions might prove useful for later generation syntheses towards the enantioselective total synthesis of lyngbyatoxin A.



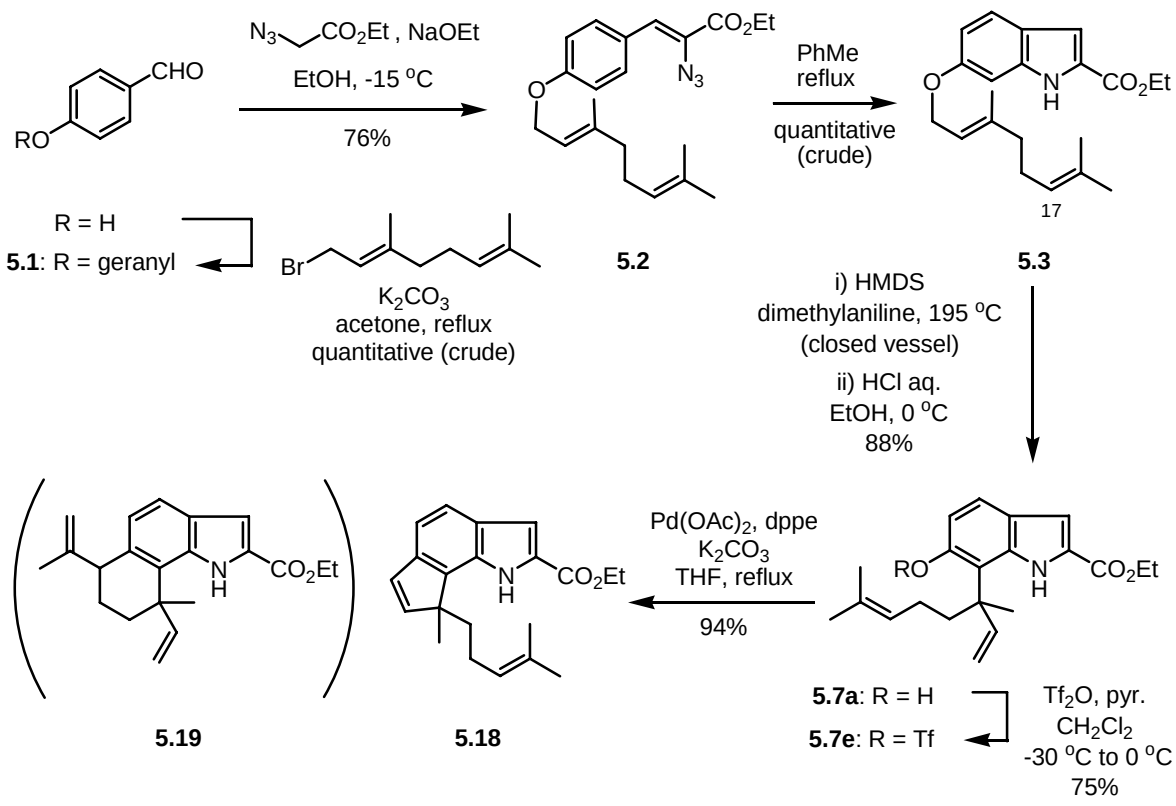

**Scheme 6.3** Preparation of (**6.2**) *via* a Cu-catalyzed asymmetric allylic substitution.

The construction of the teleocidins B's core was also investigated (Scheme 6.4). *para*-Geranyloxybenzaldehyde (**5.1**), readily obtained from *para*-hydroxybenzaldehyde and geranyl bromide in excellent yield, was converted into the corresponding azidocinnamate (**5.2**) in 76% yield upon treatment with ethyl azido acetate. Thermolysis of the latter in toluene afforded the test indole (**5.3**) quantitatively. A regioselective, high-yielding aromatic Claisen rearrangement afforded 6-hydroxyindole (**5.7a**), which contains the C-14 quaternary stereocenter characteristic of the teleocidins B. Importantly, and in order to suppress the abnormal Claisen rearrangement of (**5.7a**), we found that the rearrangement reaction had to be performed in the presence of HMDS. The precursor of the key IHR, triflate (**5.7e**), was prepared from 6-hydroxyindole (**5.7a**) in good yield (75%) upon treatment with $Tf_2O$ in the presence of pyridine at low temperature. The IHR of (**5.7e**), which was expected to deliver the cyclohexadieno-indole (**5.19**) *via* a 6-*exo*-*trig* cyclization, afforded exclusively and in high yield (up to 94%) the product of a rare 5-*endo*-*trig* path, cyclopentadieno-indole (**5.18**).

---

[6.1] (a) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1457. (b) Kacprznski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676. (c) Cesati, R. R.; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96.

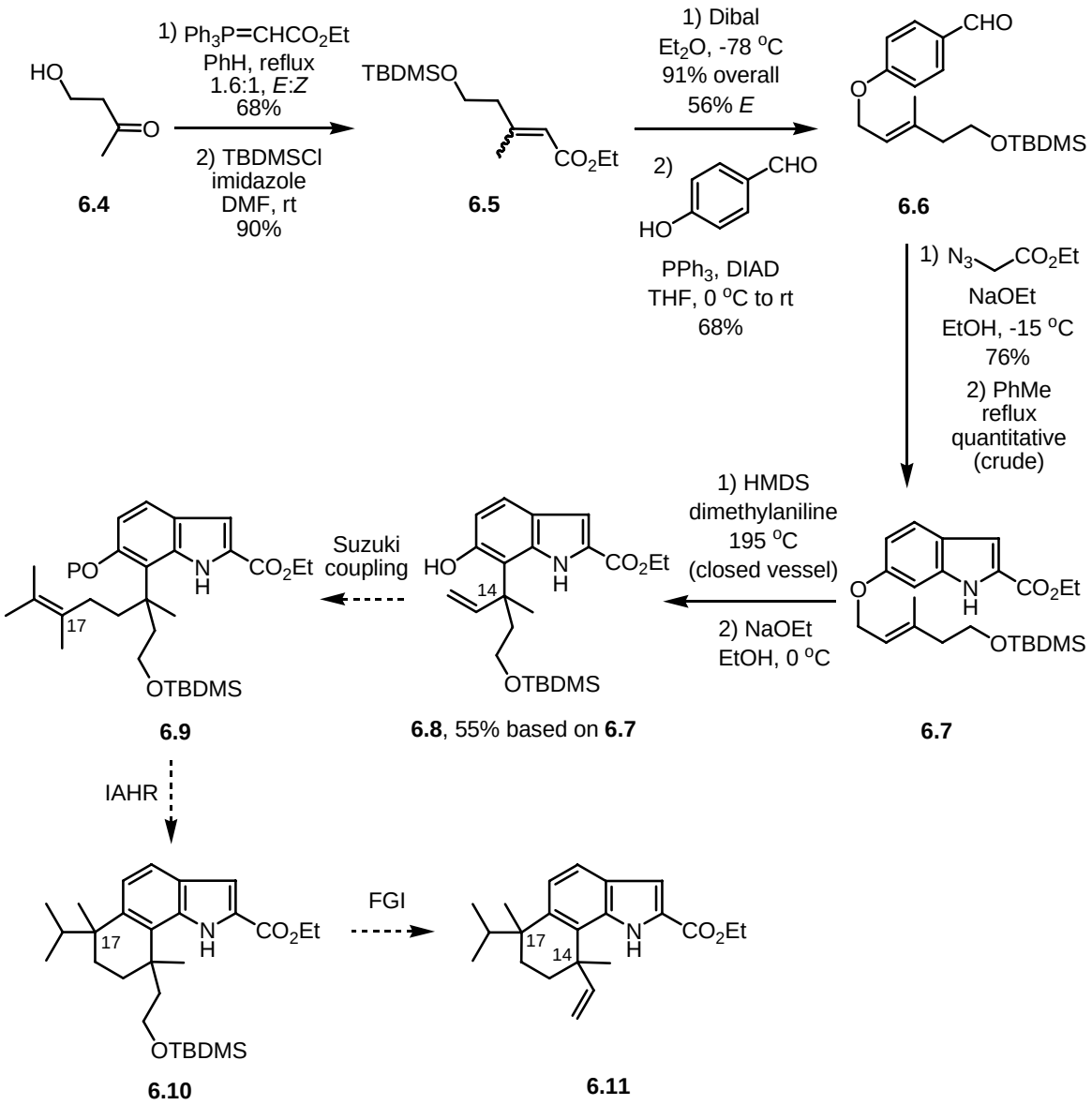
[6.2] The Knochel group has also disclosed a similar approach based on a copper mediated $S_N2'$ substitution of pentafluorobenzoates with diorganic zinc reagents: Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 4627.




**Scheme 6.4** Preparation of cyclopentadiene-indole (**5.18**).

Although mechanistically interesting, the formation of cyclopentadieno-indole (**5.18**) represents a setback with respect to the planned construction of the carbocyclic framework of the teleocidins B and, from a synthetic point of view, it implies that the vinylic double bond at the C-14 quaternary carbon has to be installed at a later stage with respect to the key IHR.

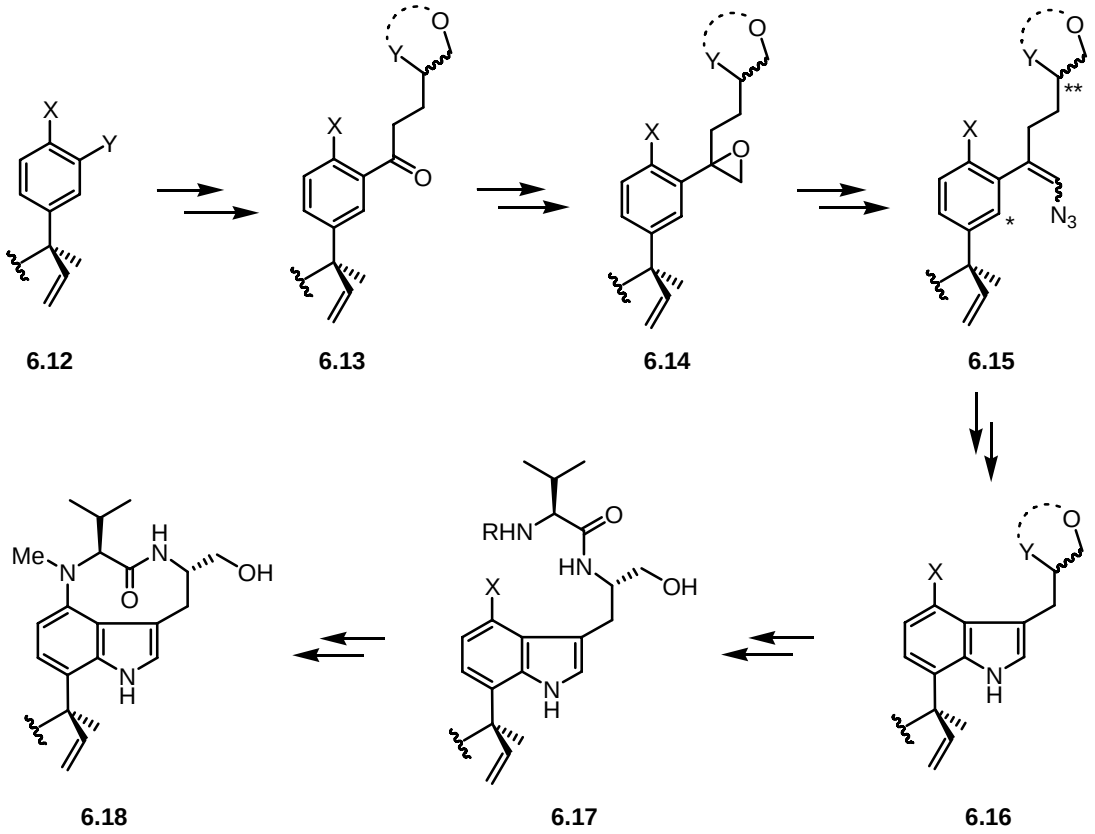
Some initial experiments towards such type of approach have already been performed and an example is shown in Scheme 6.5. In this particular case the vinyl double bond at C-14 in indole (**6.8**) was envisioned to participate in a Suzuki cross-coupling reaction which would install the required tetrasubstituted double bond at C-17. The "final" vinylic moiety at C-14 in the teleocidins B would then be obtained by functional group manipulation of the TBDMS ether appendage.




**Scheme 6.5** Preparation of indole (**6.8**).

Finally, some considerations regarding potential future work are presented. One of the main limitations of the Hemetsberger-Knittel indole synthesis in its traditional form is that only C-3 unsubstituted 2-indole carboxylates are available. Whereas functionalization of the indolic C-3 position and decarboxylation of the C-2 positions in indoles are well precedented, it would be advantageous, if only for the sake of convergence, to avoid these steps. A possible strategy that meets these requirements is shown in Scheme 6.6 exemplified for lyngbyatoxin A. The required vinyl-azide functionality for the Hemetsberger-Knittel reaction would now be accessed *via* the ring-opening of the functionalized epoxide (**6.14**) followed by an elimination reaction.

This would eliminate the need to use a benzaldehyde derivative as the starting material and, at the same time, avoid the use of an azidocarboxylate as the azide functionality precursor. An important open question at this planning stage concerns the fate of the nitrene species formed from vinyl-azide (**6.15**), which has the potential to participate in aromatic (at *) and/or aliphatic (at **) (formal) C-H insertions. In yet another bold hypothesis, the 9-membered lactam ring in (**6.18**) could conceivably be accessed *via* an intramolecular Buchwald-Hartwig amination of (**6.17**).




**Scheme 6.6** Alternative strategy to the construction of the indole nucleus and the 9-membered lactam ring in the teleocidins alkaloids.

# CHAPTER 7
# Experimental

## 7.1 - General

All moisture- and air- sensitive reactions were carried out under an argon atmosphere using oven-dried or flame-dried glassware. Reaction solvents were distilled prior to use by standard procedures. $Et_2O$, THF and toluene were distilled under nitrogen from sodium-benzophenone. $CH_2Cl_2$, $NEt_3$, pyridine and $^{i}Pr_2NH$ were distilled under nitrogen from $CaH_2$. Anhydrous DMSO, DMF and NMP were purchased from Aldrich and stored over 4Å MS under argon. $^{1}$H-NMR (200 MHz, 300 MHz and 500 MHz) and $^{13}$C-NMR (75 MHz and 125 MHz) spectra were recorded on either a Bruker AC-200 (200 MHz), a Varian Mercury 300 (300 MHz) or a Varian Inova 500 (500 MHz) spectrometers at ambient temperature. $^{31}$P-NMR (202 MHz) spectra were recorded on a Varian Inova 500 (500 MHz) spectrometer at ambient temperature. Chemical shifts (δ) are reported in ppm. Undeuterated solvents residues were used as internal standard (for $CHCl_3$, $^{1}$H: 7.27 ppm and $^{13}$C: 77.0 ppm; for benzene, $^{1}$H: 7.16 ppm and $^{13}$C: 128.0 ppm); for acetone, $^{1}$H: 2.13 ppm and $^{13}$C: 30.7 ppm). $H_3PO_4$ (30% aq., 0.0 ppm) was used as external standard for $^{31}$P-NMR. Coupling constants (*J*) are given in Hertz (Hz). Multiplicities of peaks are reported in the following way: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ´d´ (pseudo-doublet), ´t´ (pseudo-triplet), ´q´ (pseudo-quartet) and combinations of these. Hydrogen-tin coupling constants ($J_{H\text{-}Sn}$) are given as the average of the $^{117}$Sn and $^{119}$Sn values. Optical rotations were measured with a Perkin Elmer 241 Polarimeter at ambient temperature and the concentration (*c*) is given in g *per* 100 mL. Analytical high performance liquid chromatography (HPLC) was performed using a Varian 9012 Solvent Delivery System with a Varian 9065 Polychrom Diode Array Detector. HPLC grade solvents were obtained from LAB-SCAN. Electron impact (EI) low resolution mass spectra (LRMS) were performed with a VG Trio-2 single quadropole instrument at the Department of Chemistry, Technical University of Denmark. Melting points of crystalline materials were determined on a Heidolph capillary melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) analyses were performed using 0.25 mm Merk Kiselgel aluminum-backed 60 $F_{254}$ silica gel plates. Visualization was achieved by using (some of) the following sequential steps: i) exposure to UV light, ii) brief exposure to iodine vapors, iii) deeping on a solution of either 5-10% of phosphormolybdic acid in EtOH, basic $KnMnO_4$ or ninydridin and iv) gentle heating. Merk silica gel 60 (40-63 μm, 230-400

mesh) was used for flash chromatography purification. Preparative thin layer chromatography (PTLC) was performed on 20×20 cm, 1500 μm glass-backed plates with fluorescent indicator (Aldrich). Materials to be separated by PTLC are applied as long streaks, developed and recovered by scraping the adsorbent from the plate and eluting with EtOAc or $CH_2Cl_2$. New compounds are characterized by $^1$H- and $^{13}$C-NMR and, when relevant, microanalyses. Known compounds were characterized by $^1$H- and/or $^{13}$C-NMR. Microanalyses were performed at the Microanalysis Laboratory, Institute of Physical Chemistry, University of Vienna, Austria. Molecular sieves were dried at 150-160 $^o$C for at least 12 h and then allowed to reach room temperature under argon. Unless otherwise stated, commercially available reagents, purchased from Aldrich, Fluka, Merk or TCI were used without further purification. "Aqueous ½ saturated brine" and "aqueous 1/3 saturated $NaHCO_3$" refer to a water:brine, 1:1 (v:v) and water:saturated $NaHCO_3$, 2:1 (v:v) solutions, respectively. The following cooling baths were used: a slurry of liquid nitrogen in ether (approximately -110 $^o$C to -85 $^o$C); a slurry of dry ice in acetone (approximately -78 $^o$C); a slurry of liquid nitroge in *ortho*-dichlorobenzene (approximately -25 $^o$C). Commercial NaH (as a 60% dispersion in oil) was washed with pentane (2 portions that cover the amount of NaH dispersion used) and the last traces of pentane are removed under high vacuum.

## 7.2 – General Experimental Procedures

**Procedure for the preparation of demetallated silica gel:**
Silica gel (1 Kg) was slurried in aqueous 10% HCl (2 L). The resulting yellow aqueous layer was decanted off and the remaining silica gel was washed with 1 L batches of distilled water until the washings reached pH 4 (typically 15-20 washes are required). The obtained silica gel was then treated with a solution of aqueous 25% ammonia (1 mL) in water (1 L). The aqueous phase was decanted off and the remaining silica gel was oven-dried at 160 $^o$C for 2 days with occasional manual stirring.

### $Pd(PPh_3)_4$ Tetrakis(triphenylphosphine)palladium

Following a literature procedure,[7.1] a vigorously stirred yellow suspension of $PdCl_2$ (500 mg, 2.8 mmol, 1.0 eq.), $PPh_3$ (3.70 g, 14.1 mmol, 5.0 eq.) in dry DMSO (previously degassed by bubbling argon for approximately ½ h) was inserted in an oil bath previously heated to 150 $^oC$. After 10-15 min. at this temperature, an orange solution is obtained. The oil bath was then removed and $N_2H_4 \cdot H_2O$ (565 mg, 11.3 mmol, 4 eq.) was immediately added dropwise with vigorous gas evolution observed. After addition, the mixture was allowed to slowly reach room temperature. An initial transient black color faded away into a golden and then into a bright yellow coloration. After 5-10 min., some crystals started forming. The stirring was stopped, the reaction flask was covered with silver foil and this mixture was left to rest at room temperature under argon overnight. The obtained mixture was filtered and the resulting crystals were rinsed with cold EtOH (2 portions of 35 mL) and cold $Et_2O$ (3 portions of 15 mL). The title compound was obtained as bright yellow crystals (3.0 g, 92%) which were best kept refrigerated, under argon and protected from light. Mp 116-118 $^oC$ (lit. 116 $^oC$).

**Procedure for the preparation of a 3.8 M solution of $^t$BuOOH in toluene:**
Following a literature procedure,[7.2] an aqueous solution of 70% $^t$BuOOH (165 mL) was gently swirled/extracted with toluene (2 portions of 200 mL) (note: strong shaking should be avoided). The combined cloudy organic layers were then heated to 105-115 $^oC$ in a Dean Stark apparatus behind a safety screen until no more water condensed (typically this process was completed over 4 h, with the side-arm of the Dean Stark being empty 2-3 times during this period). The obtained solution of $^t$BuOOH in toluene was then allowed to reach room temperature, transferred into a dark bottle and kept refrigerated under argon. $^1$H-NMR showed the concentration to be approximately 3.8 M.

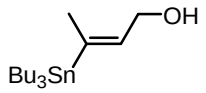
**Procedure for the preparation of sodium phenoxide:**
To an ice cold suspension of NaH (486 mg, 20.2 mmol, 1.0 eq.) in THF (13 mL) was dropwise added, over 15 min., a solution of phenol (2.0 g, 21.3 mmol, 1.05 eq.) in THF (7 mL), during which period gas evolution was observed. The resulting solution was stirred at ice bath temperature for 10 min. and at room temperature for 3 h further, after which period most of the solvent was removed under vacuum and

[7.1] Komiya, S. In "*Synthesis of Organometallic Compounds: A Practical Guide*" **1997**, Wiley: England.
[7.2] Hill, J. G.; Rossiter, B.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607.

pentane (35 mL) was added. The obtained suspension was rapidly filtrated under argon and the resulting solid was dried at 40 °C under high vacuum for 1½ h. The title compound was obtained as a white solid (2.23 g, 91%) that was stored under argon.

**Procedure for the preparation of $MnO_2$:**
Following a literature procedure,[7.3] to a vigorously stirred solution of $KMnO_4$ (67 g) in $H_2O$ (300 mL) was added absolute EtOH (100 mL) in three portions at room temperature (note: a large beaker covered with a watch glass was used). The viscous brownish mixture obtained was stirred at room temperature for 1 h, after which the stirring was stopped and the obtained suspension was allowed to rest for 45 min.. The suspension is vacuum-filtered and the dark brown solid obtained was rinsed with water (1.5 L), triturated and then heated at 125 °C under argon for 24 h, after which it was allowed to reach room temperature, triturated again and heated at 125 °C under argon for another 24 h. Obtained a dark brown/black powder (39 g) which was kept in a dark glass bottle under argon.

## 7.3 – Experimental Procedure for Chapter 3 (Lyngbyatoxin A)



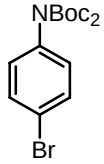

**(*E*)-3-(Tributylstannyl)but-2-en-1-ol (3.11)**

Following a literature procedure,[7.4] to a -78 °C cold solution of $(BuSn)_2$ (30.16 g, 52.0 mmol, 8.0 eq.) in THF (155 mL) was dropwise added a solution of $^{n}$BuLi in hexanes (1.6 M; 32.5 mL, 52 mmol, 8.0 eq.) over 15 min., during which period a pale yellow color developed. After stirring at -78 °C for 15 min., the temperature was allowed to reach -45 °C (by means of a cooling bath at this temperature) and stirring continued for further 35 min. at this temperature. The resulting solution was re-cooled to -78 °C and cannulated over 40 min. into a -78 °C cold, vigorously stirred, suspension of CuCN (2.3 g, 26 mmol, 4.0 eq.) in THF (26 mL). The bright yellow mixture obtained was stirred at -78 °C for 50 min., after which the temperature was allowed to reach -45 °C (by means of a cooling bath at this temperature) and stirring continued for further 45 min. at this temperature. The

[7.3] King, R. B.; Stone, F. G. A. *Inorg. Synth.* Vol. VIII, 194.
[7.4] (a) Betzer, J.-F.; Ardisson, J.; Lallemand, J.-Y.; Pancrazi, A. *Tetrahedron Letts.* **1997**, *38*, 2279. (b) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768. (c) Betzer, J.-F.; Pancrazi, A. *Synlett.*, **1998**, 1129. (d) Betzer, J.-F.; Pancrazi, A. *Synthesis*, **1999**, 629-634. (e) Dominguez, B.; Pazos, Y.; de Lera, A. R. *J. Org. Chem.* **2000**, *65*, 5917.

resulting turbid yellow solution was then re-cooled to -78 °C and MeOH (29 mL, 715 mmol, 110 eq.) was added dropwise over 10 min., during which a tanned orange color developed. After stirring at -78 °C for 5 min., the obtained solution was allowed to reach -45 °C gradually over 15 min. and then stirred at this temperature for ½ h further. The deep reddish solution obtained was re-cooled to -78 °C and a solution of freshly distilled 2-butyn-1-ol (456 mg, 6.5 mmol, 1.0 eq.) in THF (13 mL) was added dropwise over 10 min.. The resulting solution was stirred at -78 °C for 10 min., after which the temperature was allowed to reach -30 °C (by means of a cooling bath at this temperature) and the temperature was then allowed to reach -10 °C over ½ h. The deep red mixture thus obtained was left stirring at -10 °C overnight and then quenched at this temperature with brine (150 mL). The resulting mixture was extracted with $Et_2O$ (3 portions of 130 mL) and the combined organic phases were washed with brine (150 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum afforded a colorless residue that was purified by flash chromatography (demetallated silica gel; hexane→hexane: $Et_2O$, 1:1 (v:v) with 2% $Et_3N$; fast elution) to afford the title compound as a very pale yellow oil (1.73 g, 74%).

$R_f$ (hexane:EtOAc, 3:1 (v:v)) 0.77; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.75 (tq, $J$ = 1.9, 6.0 Hz, $J_{H\text{-}Sn}$ = 64.7 Hz, 1H), 4.25 (´d´, $J$ = 6.0 Hz, 2H), 1.88 (dt, $J$ = 0.9, 1.9 Hz, $J_{H\text{-}Sn}$ = 45.1 Hz, 3H), 1.42-1.55 (m, 6H), 1.24-1.38 (m, 7H), 0.82-0.94 (m, 15H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 142.7, 139.4 ($J_{C\text{-}Sn}$ = 24.2 Hz), 59.1 ($J_{C\text{-}Sn}$ = 60.6 Hz), 29.4 ($J_{C\text{-}Sn}$ = 19.7 Hz), 27.6 ($J_{C\text{-}Sn}$ = 55.1 Hz), 19.7, 13.9, 9.3 ($J_{C\text{-}Sn}$ = 323.9 Hz).

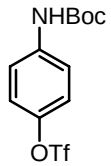



**_N,N_-(di-_tert_-Butoxycarbonly)-4-bromo-aniline (3.13a)**

A solution of _N_-(_tert_-butoxycarbonly)-4-bromo-aniline (**3.12a**) (1.0 g, 3.7 mmol, 1.0 eq.), DMAP (91 mg, 0.74 mmol, 0.2 eq.) and $Boc_2O$ (921 mg, 4.2 mmol, 1.14 eq.) in THF (7.5 mL) was refluxed for 2 days, cooled to room temperature, diluted with $Et_2O$ (70 mL) and washed with aqueous 1 M HCl (2 portions of 30 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (2 portions of 30 mL), water (20 mL), brine (20 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum afforded the title compound as a white solid (1.2 g, 90%) which was used without further purification.

$R_f$ (hexane:EtOAc, 3:1 (v:v)) 0.43 (note: the Rf values of the starting material and the product are very similar); mp 108-110 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.38-7.44 (m, 2H), 6.92-6.98 (m, 2H), 1.35 (s, 18H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 151.7, 138.7, 132.1, 129.9, 121.4, 83.3, 28.1; LRMS (EI) *m/z* = 371 $[M]^+$; Anal. Calcd. for

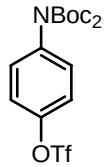
$C_{16}H_{22}BrNO_4$: C, 51.62; H, 5.96; N, 3.76. Found: C, 51.66; H, 5.77; N, 3.57.




**4-*N*-(*tert*-Butoxycarbonly)aminophenyl trifluorosulfonate (3.12c)**

To an ice cold tanned solution of 4-*N*-(*tert*-butoxycarbonly)amino phenol (**3.12b**) (3.2 g, 15.3 mmol, 1.0 eq.) in pyridine (22 mL) was dropwise added $Tf_2O$ (2.98 mL, 17.6 mmol, 1.15 eq.). The resulting solution was stirred at 0 °C for 45 min., after which it was allowed to reach room temperature and stirred for further ½ h. The obtained solution was re-cooled to 0 °C, after which water (50 mL) was added and this mixture was vigorously stirred for 45 sec., during which period a heavy precipitate formed. The mixture was partitioned between $Et_2O$ (200 mL) and water (30 mL) and the aqueous layer was further extracted with $Et_2O$ (20 ml). The combined organic layers were washed with aqueous 10% HCl (2 portions of 100 mL), water (50 mL), brine (30 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure afforded the title compound as a beige solid (4.7 g, 90%) which was used without further purification.

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.6; mp 96-98 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.41-7.47 (m, 2H), 7.15-7.21 (m, 2H), 6.63 (brs, 1H), 1.51 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 152.6, 144.7, 138.7, 122.2, 119.7, 81.5, 54.7, 28.5; Anal. Calcd. for $C_{12}H_{14}F_3NO_5S$: C, 42.23; H, 4.13; N, 4.10. Found: C, 42.34; H, 3.98; N, 4.01.

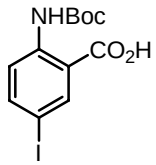



**4-*N*,*N*-(di-*tert*-Butoxycarbonly)aminophenyl trifluorosulfonate (3.13b)**

A solution of 4-*N*-(*tert*-butoxycarbonly)aminophenyl trifluorosulfonate (**3.12c**) (1.25 g, 3.7 mmol, 1.0 eq.), DMAP (91 mg, 0.74 mmol, 0.2 eq.) and $Boc_2O$ (921 mg, 4.2 mmol, 1.14 eq.) in THF (7.5 mL) was refluxed for 2 days, cooled to room temperature, diluted with $Et_2O$ (70 mL) and washed with aqueous 1 M HCl (2 portions of 30 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (2 portions of 30 mL), water (20 mL), brine (20 mL) and dried ($MgSO_4$). Removal of the solvent under vacuum afforded the title compound as a light tanned solid (1.4 g, 86%) which was used without further purification.

$R_f$ (hexane:EtOAc, 5:1 (v:v)) 0.37 (note: the Rf values of the starting material and the product are very similar); mp 68-70 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.19-7.30 (m, 4H), 1.40 (s, 18H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 151.4, 148.4, 139.6, 130.1, 121.9, 121.1, 83.6, 28.1; Anal. Calcd. for $C_{17}H_{22}F_3NO_7S$: C, 46.26; H, 5.02; N, 3.17. Found:

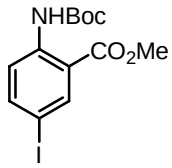
C, 46.44; H, 4.89; N, 3.07.




**2-*N*-(*tert*-Butoxycarbonyl)amino-5-iodobenzoic acid**

To a deep tanned solution of *para*-iodo anthranilic acid (5.0 g, 19.0 mmol, 1.0 eq.), $NEt_3$ (2.8 ml, 38 mmoL, 2 eq.) in MeOH (25 mL) was added $Boc_2O$ (5.0 g, 22.8 mmol, 1.2 eq.). The resulting solution was refluxed for 7 h, after which it was concentrated under vacuum to afford an oily residue, which was then taken in aqueous 1 M HCl (400 mL) and extracted with EtOAc (2 portions of 150 mL). The combined organic phases were washed with aqueous 1 M HCl (2 portions of 150 mL), water (2 portions of 150 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure affording the title compound as a pale yellow solid (4.86 g, 70%) which was used without further purification.

$R_f$ ($^i$PrOH:aqueous 25% ammonia, 7:3 (v:v)) 0.66; mp 189-190 $^o$C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.39 (brs, 1H), 8.37 (d, *J* = 2.2 Hz, 1H), 8.26 (d, *J* = 9.0 Hz, 1H), 7.77 (dd, *J* = 2.2, 9.0 Hz, 1H), 1.52 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 168.6, 152.7, 143.0, 142.5, 139.9, 120.7, 116.3, 83.1, 80.8, 28.3; Anal. Calcd. for $C_{12}H_{14}INO_4$: C, 39.69; H, 3.89; N, 3.86. Found: C, 39.60; H, 3.65; N, 3.71.

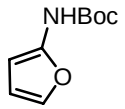



**Methyl 2-*N*-(*tert*-butoxycarbonyl)amino-5-iodobenzoate (3.14)**

To an ice cold suspension of 2-*N*-(*tert*-butoxycarbonyl)amino-5-iodobenzoic acid (3.0 g, 8.26 mmol, 1.0 eq.) and $Cs_2CO_3$ (1.35 g, 4.13 mmol, 0.5 eq.) in DMF (17 mL) was dropwise added MeI (0.51 mL, 8.26 mmol, 1.0 eq.). The temperature was allowed to reach room temperature and stirring continued for 20 h (for convenience), after which most of the DMF was removed under reduced pressure. The obtained residue was taken up in EtOAc (120 mL), the cesium salts were removed by filtration and the filtrate was concentrated under vacuum to afford the title compound as a viscous oil that upon standing crystallizes as a light tanned solid (1.87 g, 60% crude) which was used without further purification.

$R_f$ ($^i$PrOH: aqueous 25% ammonia, 7:3 (v:v)) 0.69; mp 78-80 $^o$C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.19 (brs, 1H), 8.26 (d, *J* = 2.2 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 7.73 (dd, *J* = 2.2, 9.0 Hz, 1H), 3.90 (s, 3H), 1.51 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 167.5, 152.8, 143.1, 142.2, 139.5, 121.0, 116.3, 83.4, 81.1, 52.7, 28.5; LRMS (EI) *m/z* = 377 $[M]^+$; Anal. Calcd. for $C_{13}H_{16}INO_4$: C, 41.40; H, 4.28; N, 3.71. Found: C,

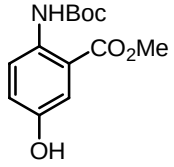
41.13; H, 3.98; N, 3.54.



**2-*N*-*tert*-butoxycarbonly-aminofurane**

Following a literature procedure,[7.5] to a pale yellow solution of 2-furanoic acid (2.0 g, 17.8 mmol, 1.0 eq.) and $NEt_3$ (5.0 mL, 35.9 mmol, 2.0 eq.) in $^t$BuOH (40 mL, 418 mmol, 23.5 eq.) was dropwise added DPPA (8.0 mL, 37.1 mmol, 2.1 eq.). The resulting solution was heated to 85 $^o$C for 12 h, after which a short path-distillation adaptor was inserted, the temperature of the heating bath was increased to 105-110 $^o$C and most of the $^t$BuOH was distilled off. The viscous tanned oil residue obtained was then purified by flash chromatography on silica gel (1$^{st}$ column eluted with hexane:EtOAc, 1:1 (v:v); 2$^{nd}$ column eluted with hexane:EtOAc, 5:1 (v:v)) affording the title compound as a white solid (2.27 g, 70%; minor impurity contamination) that is best used immediately.

$R_f$ (hexane:EtOAc, 5:1 (v:v)) 0.32; mp 97-99$^o$C (lit.: 98-99 $^o$C); $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.05 (dd, *J* = 1.0, 2.0 Hz, 1H), 6.77 (brs, 1H), 6.33 (dd, *J* = 2.0, 3.2 Hz, 1H), 6.03 (brs, 1H), 1.50 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 151.9, 145.3, 136.0, 111.1, 95.0, 81.3, 28.2.



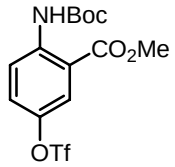
**Methyl 2-*N*-(*tert*-butoxycarbonyl)amino-5-hydroxybenzoate (3.15)**

Following a literature procedure,[7.5] a pale yellow solution of 2-*N*-Boc-aminofurane (1.5 g, 8.2 mmol, 1.0 eq.) and methylpropiolate (1.44 g, 17.1 mmol, 2.0 eq.) in benzene (15 mL) was refluxed for 20 h, after which a second amount of methypropiolate (0.7 g, 8.2 mmol, 1.0 eq.) in benzene (5 mL) was added and reflux continued for 20 h further. Upon reaching room temperature, the deep reddish solution becomes a suspension which was then diluted with cold toluene (5 mL) and filtered. The solid thus obtained was rinsed with cold toluene (2 portions of 3 mL) affording the title compound a white solid (695 mg). The mother liquor was concentrated under vacuum and the residue obtained was purified by flash chromatography on silica gel (hexane:EtOAc, 2:1 (v:v)) further delivering the wanted compound as a very pale yellow solid (302 mg). Combined yield: 997 mg, 45%.

$R_f$ (hexane:EtOAc, 2:1 (v/v)) 0.27; mp 137-139 $^o$C (lit.: 138-139 $^o$C); $^1$H-NMR

[7.5] Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088.

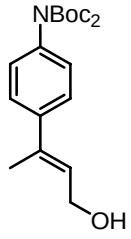
($CDCl_3$, 300 MHz) δ 9.94 (brs, 1H), 8.23 (d, *J* = 9.1 Hz, 1H), 7.45 (d, *J* = 3.1 Hz, 1H), 7.01 (dd, *J* = 3.1, 9.1 Hz, 1H), 5.46 (brs, 1H), 3.89 (s, 3H), 1.52 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 168.3, 153.5, 149.9, 135.8, 122.3, 120.9, 116.8, 115.8, 80.7, 52.5, 28.6.




**Methyl 2-*N*-(*tert*-butoxycarbonyl)amino-5-(trifluoromethyl-sulfonyloxy)benzoate (3.16)**

To an ice cold yellow solution of methyl 2-*N*-(*tert*-butoxycarbonyl)amino-5-hydroxybenzoate (**3.15**) (300 mg, 1.1 mmol, 1.0 eq.) in pyridine (2 mL) was dropwise added $Tf_2O$ (217 µL, 1.29 mmol, 1.15 eq.) and the resulting orange solution was stirred at ice bath temperature for 10 min., after which it was it was allowed to reach room temperature and stirred for further 1½ h. The obtained solution was re-cooled to 0 °C, water (10 mL) was added and this mixture was vigorously stirred for 45 sec. during which period a heavy precipitate formed. The mixture was partitioned between $Et_2O$ (40 mL) and water (5 mL) and the aqueous layer was extracted with $Et_2O$ (2 portions of 10 ml). The combined organic layers were washed with aqueous 10% HCl (2 portions of 25 mL), water (20 mL), brine (20 mL) and dried ($Na_2SO_4$). Removal of the solvent under reduced pressure afforded the title compound as a yellow solid (414 mg, 93%), which was used without further purification.

$R_f$ (hexane:EtOAc, 2:1 (v:v)) 0.41; mp 78-80 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.32 (brs, 1H), 8.59 (d, *J* = 9.4 Hz, 1H), 7.90 (d, *J* = 3.0 Hz, 1H), 7.39 (dd, *J* = 3.0, 9.4 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 1.53 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 167.2, 152.8, 142.7, 142.6, 127.4, 123.8, 120.7, 115.4, 81.5, 53.0, 28.5; Anal. Calcd. for $C_{14}H_{16}F_3NO_7S$: C, 42.11; H, 4.04; N, 3.51. Found: C, 42.29; H, 3.91; N, 3.42.

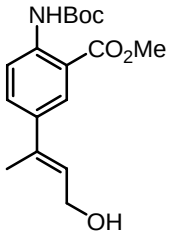



**(*E*)-4-(4-Hydroxybut-2-en-2-yl)-*N*,*N*-di-*tert*-butoxy-phenyl carbamate (3.17)**

A solution of *N*,*N*-(di-*tert*-butoxycarbonly)-4-bromo-aniline (**3.13a**) (118 mg, 0.32 mmol, 1.15 eq.), $Pd_2(dba)_3{\cdot}CHCl_3$ complex (20 mg, 0.02 mmol, 6 mol%), $AsPh_3$ (19 mg, 0.06 mmol, 20 mol%), CuI (10 mg, 0.05 mmol, 15 mol%) and (*E*)-3-(tributylstannyl)but-2-en-1-ol (**3.11**) (100 mg, 0.28 mmol, 1.0 eq.) in toluene (1.3 mL) was heated to 95 °C to 100 °C for 24 h (for convenience). The resulting tanned mixture was concentrated under vacuum and the resulting residue was purified by flash chromatography on silica gel (hexane:EtOAc,

1:1 (v:v)) to afford the title compound as a pale yellow oil (37 mg, 32%).

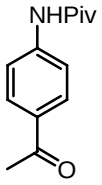
$R_f$ (hexane:EtOAc, 2:1 (v:v)) 0.13; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.36-7.41 (m, 2H), 7.05-7.12 (m, 2H), 5.99 (tq, *J* = 1.3, 6.8 Hz, 1H), 4.35 (dd, *J* = 0.6, 6.8 Hz, 2H), 2.06 (dt, *J* = 0.6, 1.3 Hz, 3H), 1.42 (s, 18H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 152.2, 142.0, 138.5, 137.2, 127.9, 127.1, 126.3, 83.0, 60.2, 28.1, 16.2; LRMS (EI) *m/z* = 363 $[M]^+$.




**(*E*)-Methyl 2-*N*-(*tert*-butoxycarbonyl)amino-5-(4-hydoxybut-2-en-yl)benzoate (3.18)**

A suspension of methyl 2-*N*-(*tert*-butoxycarbonyl)amino-5-iodobenzoate (**3.14**) (95 mg, 0.25 mmol, 1.0 eq.), (*E*)-3-(tributylstannyl)but-2-en-1-ol (**3.11**) (100 mg, 0.27 mmol, 1.1 eq.), $Pd_2(dba)_3{\cdot}CHCl_3$ complex (31 mg, 0.03 mmol, 12 mol%), $AsPh_3$ (37 mg, 0.12 mmol, 48 mol%) and CuI (15 mg, 0.08 mmol, 30 mol%) in NMP (1.5 mL) was inserted into an oil bath previously heated to 50 °C to 60 °C and stirred at this temperature for 20 h. The resulting black mixture was poured into aqueous KF (15 mL) and stirred vigorously for 4 min., after which $Et_2O$ (15 mL) was added and the layers separated. The aqueous layer was further extracted with $Et_2O$ (2 portions of 5 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was removed under vacuum to afford an oily residue that was purified by flash chromatography on silica gel (hexane:EtOAc, 1:1 (v:v) with 2% $NEt_3$). The title compound was obtained as a tan oil (36 mg, 56%).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.28; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.24 (brs, 1H), 8.38 (d, *J* = 8.9 Hz, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.55 (dd, *J* = 2.4, 8.9 Hz, 1H), 5.97 (tq, *J* = 1.2, 6.7 Hz, 1H), 4.35 (d, *J* = 6.7 Hz, 2H), 3.91 (s, 3H), 2.05 (d, *J* = 1.2 Hz, 2H), 1.52 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 168.8, 153.1, 141.5, 136.5, 135.7, 131.9, 128.1, 126.2, 118.8, 114.3, 80.8, 60.1, 52.5, 28.5, 16.0; LRMS (EI) *m/z* = 321 $[M]^+$.




***N*-(4-Acetylphenyl)pivalamide (3.19)**

Following a literature procedure,[7.6] to an ice cold tanned solution of 4-aminoacetophenone (15 g, 111 mmol, 1.0 eq.) in pyridine (110 mL) was dropwise added PivCl (15 mL, 122 mmol, 1.1 eq.). Towards the end of

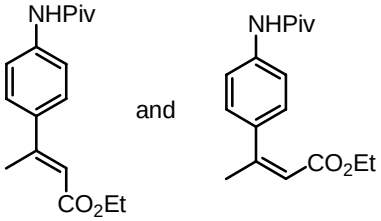
[7.6] Akama, T.; Shida, Y.; Sugaya, T.; Ishida, H.; Gomi, K.; Kasai, M. *J. Med. Chem.* **1996**, *39*, 3461.

addition, a precipitate started to form. The suspension was allowed to reach room temperature and stirring continued for further 4 h, after which it was partitioned between EtOAc (300 mL) and water (300 mL). The aqueous layer was further extracted with EtOAc (2 portions of 200 mL). The combined organic layers were washed with aqueous 2 M HCl (3 portions of 300 mL), aqueous $NaHCO_3$ (100 mL), brine (120 mL) and dried ($Na_2SO_4$). Removal of the solvent under vacuum delivered the title compound as a tan solid (23.6 g, 97%) which was used without further purification.

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.34; mp 137-140 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.92 (´d´, *J* = 8.6 Hz, 2H), 7.65 (´d´, *J* = 8.6 Hz, 2H), 7.56 (brs, 1H), 2.57 (s, 3H), 1.33 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 197.2, 177.1, 142.7, 133.0, 129.9, 119.2, 40.1, 27.8, 26.7; Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.41; H, 7.78; N, 6.36.

**General procedure for the Horner-Wadsworth-Emmons reaction of substituted acetophenones with triethylphosphonoacetate (GP 1):**

To an ice cold suspension of NaH in THF (0.5 M) was dropwise added a solution of triethylphosphonoacetate (1.15 eq.) in THF (just enough to transfer it quantitatively) with concomitant gas evolution. After stirring for 15-20 min. at 0 °C and for further 15-20 min. at room temperature, a solution of the acetophenone derivative (1.0 eq.) in THF (1 M) was added dropwise and the resulting mixture was stirred at room temperature (or, for less reactive substrates, at reflux temperature) overnight, after which it was partitioned between $Et_2O$ and aqueous ½ saturated brine. The aqueous layer was further extracted with $Et_2O$ and the combined organic phases were washed with brine, dried ($MgSO_4$) and the solvent removed under vacuum to afford a mixture of the (*E*)- and (*Z*)- isomers, which could be separated by (repeated) flash chromatography on silica gel.



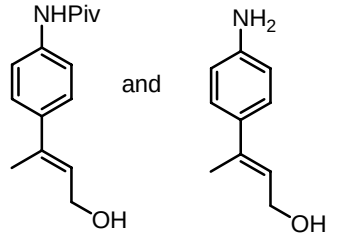

**(*E*)-Ethyl 3-(4-pivalamidophenyl)but-2-enoate (3.20)**
and
**(*Z*)-Ethyl 3-(4-pivalamidophenyl)but-2-enoate (3.20)**

Following GP 1, using *N*-(4-acetylphenyl) pivalamide (**3.19**) (1.5 g, 6.84 mmol) and refluxing the reaction mixture overnight. Purification by (repeated) flash chromatography on silica gel (hexane:$Et_2O$, 1:1 (v:v)→hexane:$Et_2O$, 1:2 (v:v))

delivered pure (*E*)-(**3.20**) (1.32 g, 67% as a white solid) and (*Z*)-(**3.20**) (340 mg, 17% as a white solid) isomers. Combined yield: 84%.
For (*E*)-Ethyl 3-(4-pivalamidophenyl)but-2-enoate (**3.20**): $R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.49; mp 101-102 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.52-7.58 (m, 2H), 7.44-7.50 (m, 2H), 7.37 (brs, 1H), 6.13 (´d´, *J* = 1.2 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.56 (d, *J* = 1.2 Hz, 3H), 1.28-1.34 (m, 12H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 176.9, 167.2, 154.8, 139.1, 137.8, 127.3, 119.8, 116.4, 60.1, 39.9, 27.8, 17.9, 14.6; LRMS (EI) *m/z* = 289 $[M]^+$; Anal. Calcd. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.75; H, 7.99; N, 4.76.

For (*Z*)-Ethyl 3-(4-pivalamidophenyl)but-2-enoate (**3.20**): $R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.45; mp 82-84 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.49-7.56 (m, 2H), 7.32 (brs, 1H), 7.16-7.22 (m, 2H), 5.88 (´d´, *J* = 1.4 Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 2.15 (d, *J* = 1.4 Hz, 3H), 1.31 (s, 9H), 1.13 (t, *J* = 7.1 Hz, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 177.0, 166.2, 155.0, 137.9, 136.6, 128.0, 119.4, 117.8, 60.0, 39.9, 27.9, 27.2, 14.3; LRMS (EI) *m/z* = 289 $[M]^+$ ; Anal. Calcd. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.79; H, 8.14; N, 4.82.

**General procedure for the Dibal reduction of *α,β*-unsaturated esters to the corresponding allylic alcohols (GP 2):**
To an ice cold solution of the *α,β*-unsaturated ester (1.0 eq.) in $Et_2O$ (0.4 M) was dropwise added a solution of Dibal in hexane (2.0 eq.). The obtained solution was allowed to reach room temperature and stirred for approximately 2 h, after which it was re-cooled to ice bath temperature and diluted with $Et_2O$, followed by slow addition of brine. After vigorous stirring for 5-10 min., a gel-like biphasic system typically formed. Aqueous 4 M HCl was then carefully added and the mixture was stirred at 0 °C for 10 min. and then at room temperature until a clear biphasic system was obtained (typically 15 min. further). After separation of the layers, the aqueous layer was further extracted with $Et_2O$ and the combined organic phases were washed with brine and dried ($MgSO_4$). Evaporation of the solvent under vacuum followed by purification by flash chromatography on silica gel afforded the corresponding allylic alcohol.

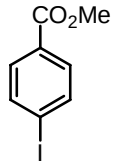



**(*E*)-*N*-(4-(4-Hydroxybut-2-en-2-yl)phenyl)pivalamide (3.21)**
and
**(*E*)-3-(4-Aminophenyl)but-2-en-1-ol (3.22)**

The following modification of GP 2 was used: to a -78 °C cold solution of (*E*)-ethyl 3-(4-pivalamidophenyl)but-2-enoate (**3.20**) (1.2 g, 4.15 mmol, 1.0 eq.) in $CH_2Cl_2$ (19 mL) was dropwise added in three portions a solution of Dibal in hexane (1.0 M, 10.4 mL, 2.5 eq.), with 5 min. intervals between portions. The resulting reddish mixture was then stirred at -78 °C for 4½ h, after which it was quenched at this temperature by slow addition of MeOH (6 mL). The cooling bath was replaced by an ice bath, and after stirring at approximately 0 °C for 10 min, a saturated Rochelle salt aqueous solution (25 mL) was added. The resulting yellow gel-like mixture was left stirring overnight after which a homogenous biphasic system was obtained. The phases were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 portions of 15 mL). The combined organic layers were washed with Rochelle salt (30 mL), water (20 mL), brine (30 mL) and dried ($Na_2SO_4$). Removal of the solvent under vacuum afforded a tanned oil residue. Purification by flash chromatography on silica gel (hexane:EtOAc, 1:2 (v:v)) delivered (*E*)-*N*-(4-(4-hydroxybut-2-en-2-yl)phenyl) pivalamide (**3.21**) as tan solid (636 mg, 62%) and (*E*)-3-(4-aminophenyl)but-2-en-1-ol (**3.22**) as a deep tan solid (82 mg, 12%).

For (*E*)-*N*-(4-(4-hydroxybut-2-en-2-yl)phenyl) pivalamide (**3.21**): $R_f$ (hexane:EtOAc, 1:2 (v:v)) 0.35; mp 121-123 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.45-7.50 (m, 2H), 7.41 (brs, 1H), 7.32-7.37 (m, 2H), 5.94 (tq, *J* = 0.5, 6.7 Hz, 1H), 4.34 (´d´, *J* = 6.7 Hz, 2H), 2.03 (td, *J* = 0.5, 0.7 Hz, 3H), 1.84 (brs, 1H), 1.30 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 176.9,138.9, 137.4, 137.2, 126.4, 126.1, 120.0, 60.1, 39.8, 27.8, 16.1; LRMS (EI) *m/z* = 247 $[M]^+$; Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.81; H, 8.62; N, 5.62.

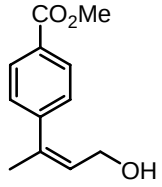
For (*E*)-3-(4-aminophenyl)but-2-en-1-ol (**3.22**): $R_f$ (hexane:EtOAc, 1:2 (v:v)) 0.29; mp 64-66 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.21-7.26 (m, 2H), 6.61-6.67 (m, 2H), 5.89 (tq, *J* = 0.6, 6.9 Hz, 1H), 4.32 (´d´, *J* = 6.9 Hz, 2H), 2.03 (´d´, *J* = 0.6 Hz, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 145.9, 137.7, 133.3, 126.9, 123.9, 115.1, 60.1, 16.0; LRMS (EI) *m/z* = 163 $[M]^+$.



**Methyl 4-iodobenzoate**

A solution of 4-iodobenzenzoic acid (15.0 g, 60.48 mmol), MeOH (240 mL) and concentrated $H_2SO_4$ (approximately 60 drops) was refluxed for 17 h, after it was allowed to slowly reach room temperature without stirring, during which period crystal formation occurred. An ice bath was then inserted for ½ h to complete this process. After filtration and washing of the crystals with cold MeOH (2 portions of 20 mL), the title compound was obtained as white needles (11.9 g). The mother liquor from filtration was concentrated under vacuum almost to dryness and the solid residue obtained was dissolved in $Et_2O$ (200 mL) and washed with saturated aqueous $NaHCO_3$ (2 portions of 50 mL) followed by water (2 portions of 50 mL), brine (50 mL) and dried ($Na_2SO_4$). Removal of the solvent under vacuum afforded a second crop of white crystals (3.6 g). Combined yield: 15.5 g, 98%.

$R_f$ ($^i$PrOH:ammonia, 7:3 (v:v)) 0.83; mp 114-116 $^o$C; $^1$H-NMR (d-acetone, 300 MHz) δ 7.92-7.96 (m, 2H), 7.75-7.80 (m, 2H), 3.89 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 166.1, 138.1, 131.1, 130.1, 100.4, 51.9; LRMS (EI) *m/z*: 262 $[M]^+$.



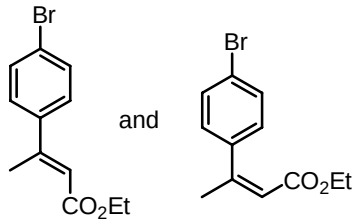
**(*Z*)-Methyl 4-(4-hydroxybut-2-en-2-yl)benzoate (3.23)**

Following a literature procedure,[7.7] NaOMe (155 mg, 2.87 mmol, 0.11 eq.) was added to a solution of $LiAlH_4$ in THF (1 M, 38.2 mL, 38.2 mmol, 1.43 eq.). The mixture was cooled to ice bath temperature and a solution of but-2-yn-1-ol (2.7 g, 38.2 mmol, 1.43 eq.) in THF (38 mL) was added dropwise over 25 min. with concomitant gas evolution. After stirring at 0 $^o$C for 5 min, the mixture was allowed to reach room temperature and stirred for further 4½ h. The white suspension obtained was re-cooled to ice bath temperature and dimethyl carbonate (3.8 g, 41.9 mmol, 1.57 eq.) was added. The resulting mixture was stirred without cooling for 10 min. during which period a pale yellow color developed. Methyl 4-iodobenzoate (7.0 g, 26.7 mmol, 1.0 eq.) was then added in one portion, immediately followed by $Pd_2dba_3{\cdot}CHCl_3$ complex (692 mg, 0.67 mmol, 2.5 mol%), $ZnCl_2$ (2.18 g, 16.0 mmol, 60 mol%) (slightly exothermic process) and $AsPh_3$ (818 mg, 2.67 mmol, 10 mol%). The resulting dark mixture was left stirring at room temperature over 2 h and then heated to gentle reflux for 2 h further. MeOH (25 mL) was then added at 0 $^o$C and the obtained mixture was left stirring at room temperature

[7.7] Havránek, M.; Dvořák, D. *J. Org. Chem.* **2002**, *67*, 2125.

overnight, after which it was poured into ½ brine (80 mL), acidified with aqueous 5% HCl to pH 5-6 (approximately 40 mL) and, after stirring for 5 min., extracted with $Et_2O$ (2 portions of 150 ml followed by 3 portions of 80 mL). The combined reddish organic layers were dried ($MgSO_4$) and the solvent removed under vacuum to afford a dark tan oil which was purified by flash chromatography on silica gel (hexane:EtOAc, 1:1 (v:v)). The tan oil obtained was taken up in MeOH (200 mL) and to this solution was added enough charcoal. The resulting black suspension was refluxed for 40 min, allowed to reach room temperature, filtered through a Celite pad and concentrated under reduced pressure to afford a pale tan oil (4.44 g, 81%).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.31; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.97-8.03 (m, 2H), 7.21-7.27 (m, 2H), 5.76 (tq, *J* = 1.3, 7.0 Hz, 1H), 4.04 (d, *J* = 7.0 Hz, 2H), 3.91 (s, 3H), 2.08 (d, *J* = 1.3 Hz, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 167.1, 145.8, 139.3, 129.7, 129.1, 128.1, 127.5, 60.3, 52.4, 25.2.

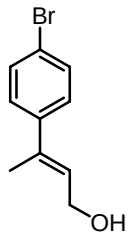



**(*E*)-Ethyl 3-(4-bromophenyl)but-2-enoate (3.24)**
and
**(*Z*)-Ethyl 3-(4-bromophenyl)but-2-enoate (3.24)**

Following GP 1, using 4-bromo-acetophenone (16.0 g, 80.4 mmol, 1.0 eq.). Purification by (repeated) column flash chromatography on silica gel (hexane: $Et_2O$, 3:1 (v:v)) delivered pure (*E*)-(**3.24**) (15 g, 70% as a colorless oil) and (*Z*)-(**3.24**) (4.5 g, 21% as a colorless oil) isomers. Combined yield: 91%.

For (*E*)-Ethyl 3-(4-bromophenyl)but-2-enoate (**3.24**): $R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.50; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.47-7.52 (m, 2H), 7.31-7.35 (m, 2H), 6.11 (q, *J* = 1.3 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 1.3 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 166.8, 154.4, 141.9, 137.8, 128.2, 117.8, 95.2, 60.2, 17.9, 14.5; LRMS (EI) *m/z* = 268 $[M-H]^+$; Anal. Calcd. for $C_{12}H_{13}BrO_2$: C, 53.55; H, 4.87. Found: C, 53.44; H, 4.59.

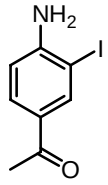
For (*Z*)-Ethyl 3-(4-bromophenyl)but-2-enoate (**3.24**): $R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.42; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.45-7.49 (m, 2H), 7.06-7.10 (m, 2H), 5.92 (q, *J* = 1.4 Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 2.15 (d, *J* = 1.4 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 165.9, 154.5, 139.9, 131.3, 128.8, 122.0, 118.5, 60.1, 27.3, 14.3.




**(*E*)-3-(4-Bromophenyl)but-2-en-1-ol (3.25)**

Following GP 2, using (*E*)-ethyl 3-(4-bromophenyl)but-2-enoate (**3.24**) (14.9 g, 55.4 mmol, 1.0 eq.). Purification by flash chromatography on silica gel (hexane:EtOAc, 1:1 (v:v)) delivered the title compound as a white solid (12.6 g, quantitative).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.29; mp 60-62 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.42-7.46 (m, 2H), 7.24-7.29 (m, 2H), 5.96 (tq, *J* = 1.3, 6.6 Hz, 1H), 4.35 (d, *J* = 6.6 Hz, 2H), 2.05, (d, *J* = 1.3 Hz, 3H), 1.56 (brs, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 141.9, 136.9, 131.6, 127.6, 127.3, 121.4, 60.1, 16.2; EI-MS *m/z*: 226 [$M^+$]; Anal. Calcd. for $C_{10}H_{11}BrO$: C, 52.89; H, 4.88. Found: C, 52.99; H, 4.84.




**4-Acetyl-2-iodoaniline (3.26)**

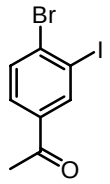
**Procedure 1** (to be preferred)**:** Following a literature procedure,[7.8] a solution of $CaCO_3$ (11.6 g, 116.0 mmol, 1.57 eq.) in water (29.5 mL) was added to a solution of *para*-acetylaniline (10 g, 74.0 mmol) in methanol (49 mL), followed by a solution of ICl (12.7 g, 78.5 mmol, 1.06 eq.) in methanol (49 mL). The mixture was stirred at room temperature for 15 h, then diluted with $Et_2O$ (300 mL) and water (50 mL). The aqueous layer was extracted with $Et_2O$ (2 portions of 100 mL) and the combined organic phases were dried ($Na_2SO_4$). Removal of the solvent in vacuum afforded a residue that was purified by column chromatography (hexane:EtOAc, 1:1 (v:v)). The title compound was obtained as a tan viscous oil which upon standing in the cold crystallizes as a yellow solid (16.6 g, 86%).

**Procedure 2:** a solution of ICl (13.2 g, 81.3 mmol, 1.1 eq.) in glacial acetic acid (420 mL) was added to a solution 4-acetylaniline (10 g, 74.0 mmol) in glacial acetic acid (500 mL) over 15 min.. After stirring at room temperature for 1½ h, the deep tanned solution was concentrated to 1/3 of its original volume and then diluted with iced water (600 mL) and $CH_2Cl_2$ (450 mL). To this biphasic system was then added, with vigorous stirring, solid $NaHCO_3$ (caution: strong gas evolution!) until the aqueous layer reaches neutral pH. The aqueous layer was extracted with $CH_2Cl_2$ (2 portions of 100 mL) and the combined deep red organic layer was washed with aqueous saturated $NaHCO_3$ (2 portions of 150 mL), aqueous ½ saturated $Na_2S_2O_3$ (200 mL), water (120 mL), brine (120 mL) and dried ($Na_2SO_4$). The solvent was removed under vacuum

[7.8] Fujita, K.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785.

and the tan paste obtained was purified by flash chromatography (hexane:EtOAc, 1:1 (v:v)) to afford a tanned thick oil which upon standing in the cold crystallizes as a yellow solid (11.9 g, 62%).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.44; mp 50-53 °C (lit. 50-52 °C); $^1$H-NMR($CDCl_3$, 300 MHz) δ 8.26 (d, *J* = 2.0 Hz, 1H), 7.75 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 2.48 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ: 195.5, 151.2, 140.6, 130.5, 129.4, 113.3, 82.8, 26.3;

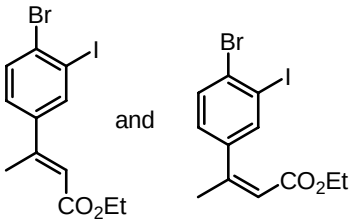



**4-Bromo-3-iodoacetophenone (3.27)**

**Part I-Preparation of the diazonium salt:** To a -10 °C cold suspension of 4-acetyl-2-iodoaniline (**3.26**) (8.45 g, 32.3 mmol) in aqueous 47% HBr (77 mL) was dropwise added over 15 min. a solution of $NaNO_2$ (2.65 g, 38.0 mmol, 1.18 eq.) in water (35 mL). The deep tanned mixture obtained was stirred for 10 min. at this temperature, after which the temperature was allowed to increase to -5 °C→0 °C and stirring continued for further 1½ h. The obtained mixture was then kept at ice bath temperature.

**Part II-Sandmeyer reaction:** To a vigorously stirred (purple) mixture of CuBr (5.57 g, 38.8 mmol, 1.2 eq.) in aqueous 47% HBr (42 mL) at 60 °C was portionwise added over 50 min. the above diazonium suspension (caution: significant frothing occurred during additions), after which the temperature was increased to 80 °C and stirring continued for further 25 min.. The resulting dark mixture was cooled to ice bath temperature and partitioned between water (400 mL) and EtOAc (400 mL). The aqueous layer was extracted with EtOAc (2 portions of 150 mL) and the combined organic layers were washed with aqueous 1 M HCl (300 mL), aqueous saturated $NaHCO_3$ (200 mL), aqueous ½ saturated brine (250 mL), dried ($MgSO_4$) and concentrated under vacuum to afford a light tan solid residue which was purified by flash chromatography (hexane:EtOAc, 1:1 (v:v)). The title compound was obtained as a pale yellow solid (9.0 g, 86%).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.55; mp 79-82 °C; $^1$H-NMR($CDCl_3$, 300 MHz) δ 8.39 (d, *J* = 2.0 Hz, 1H), 7.76 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 2.57 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 196.0, 140.3, 137.1, 135.7, 133.1, 129.1, 101.9, 26.8; LRMS (EI) *m/z* = 324 $[M]^+$; Anal. Calcd. for $C_8H_6BrIO$: C, 29.57; H, 1.86. Found: C, 29.18; H, 2.01.

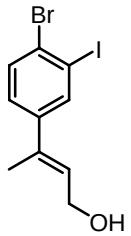



**(*E*)-Ethyl 3-(4-bromo-3-iodophenyl)but-2-enoate (3.28)**
and
**(*Z*)-Ethyl 3-(4-bromo-3-iodophenyl)but-2-enoate (3.28)**

Following GP 1, using 4-bromo-3-iodoacetophenone (**3.27**) (7.98 g, 24.6 mmol, 1.0 eq.). Purification by (repeated) flash chromatography (hexane: $Et_2O$, 3:1 (v:v)) delivered pure (*E*)-(**3.28**) (6.2 g, 64% as a white solid) and (*Z*)-(**3.28**) (1.7 g, 17% as a yellow oil) isomers. Combined yield: 81%.

For (*E*)-Ethyl 3-(4-bromo-3-iodophenyl)but-2-enoate (**3.28**): $R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.51; mp 39-42 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.93 (d, *J* = 2.2 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.28 (dd, *J* = 2.2, 8.3 Hz, 1H), 6.08 (q, *J* = 1.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.50 (d, *J* = 1.3 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 2H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 166.5, 152.8, 142.8, 138.2, 132.8, 130.5, 127.5, 118.6, 101.7, 60.4, 18.0, 14.6; LRMS (EI) *m/z* = 394 $[M]^+$; Anal. Calcd. for $C_{12}H_{12}BrIO_2$: C, 36.49; H, 3.06. Found: C, 36.63; H, 3.15.

For (*Z*)-Ethyl 3-(4-bromo-3-iodophenyl)but-2-enoate (**3.28**): $R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.40; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, *J* = 2.1 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.05 (dd, *J* = 2.1, 8.2 Hz, 1H), 5.91 (q, *J* = 1.5 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 2.13 (d, *J* = 1.5 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 2H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 165.6, 152.7, 141.5, 138.6, 132.3, 129.1, 128.5, 119.1, 100.9, 60.3, 27.1, 14.3; LRMS (EI) *m/z* = 394 $[M]^+$; Anal. Calcd. for $C_{12}H_{12}BrIO_2$: C, 36.49; H, 3.06. Found: C, 36.63; H, 3.15.




**(*E*)-3-(4-Bromo-3-iodophenyl)but-2-en-1-ol (3.29)**

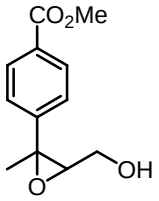
Following GP 2, using (*E*)-ethyl 3-(4-bromo-3-iodophenyl)but-2-enoate (**3.28**) (5.83 g, 14.8 mmol). Purification by flash chromatography (hexane:EtOAc, 1:1 (v:v)) afforded the title compound as a white solid (5.0 g, 96%).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.30; mp 62-64 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, *J* = 2.2 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.15 (dd, *J* = 2.2, 8.4 Hz, 1H), 5.88 (tq, *J* = 1.4, 6.6 Hz, 1H), 4.26-4.30 (m, 2H), 1.94-1.95 (m, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 143.6, 137.8, 135.5, 132.5, 128.4, 128.3, 127.1, 101.5, 60.1, 16.1; LRMS (EI)

*m/z* = 352 $[M]^+$; Anal. Calcd. for $C_{10}H_{10}BrIO$: C, 34.03; H, 2.86. Found: C, 33.98; H, 2.72.

**General procedure for the MCPBA epoxidation of allylic alcohols to the corresponding epoxides (GP 3):**

To an ice cold suspension of (commercial)[7.9] MCPBA (1.3 eq.) in $CH_2Cl_2$ (0.6 M) was dropwise added a solution of the allylic alcohol (1.0 eq.) in $CH_2Cl_2$ (0.5 M). The suspension thus obtained was stirred at ice bath temperature for 15 min. and then allowed to reach room temperature and stirred for further 2½ h, after which it was re-cooled to -5 $^oC$ and filtered through a short pad of Celite. To the filtrate was added $Ca(OH)_2$ and this suspension was stirred for 5 min. at -5 $^oC$, after which a small portion of $Na_2SO_4$ was added and stirring continued for further 5 min. at this temperature. After filtration through a short pad of Celite, the solvent was removed under vacuum. The obtained residue was usually pure enough so that it can be used directly. Occasionally, this residue was further filtered through a short column of demetallated silica gel (fast elution) affording the pure epoxide.




**(*Z*)-Methyl 4-(3-(hydroxymethyl)-2-methyloxiran-2-yl)benzoate (3.33)**

Following GP 3, using (*Z*)-methyl 4-(4-hydroxybut-2-en-2-yl)benzoate (**3.23**) (650 mg, 3.2 mmol). The title compound was obtained as a viscous yellow oil (663 mg, 93% crude).

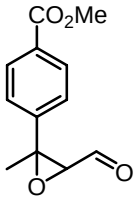
$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.22; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.96-8.02 (m, 2H), 7.37-7.42 (m, 2H), 3.90 (s, 3H), 3.42 (dd, *J* = 4.2, 11.6 Hz, 1H), 3.33 (dd, *J* = 4.2, 6.6 Hz, 1H), 3.22 (dd, *J* = 6.6, 11.6 Hz, 1H), 1.67 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 167.0, 144.2, 129.9, 129.7, 126.5, 64.8, 62.9, 61.8, 52.5, 24.5; LRMS (EI) *m/z* = 222 $[M]^+$.

**General procedure for the Swern oxidation of allylic epoxides to the corresponding epoxy-aldehydes (GP 4):**

A solution of oxalyl chloride (2.0 eq.) in $CH_2Cl_2$ (0.25 M) at -78 $^oC$ was treated dropwise with a solution of DMSO (4.0 eq.) in $CH_2Cl_2$ (5 M), during which period gas evolution was observed. After stirring at this temperature for further 15-20 min. a solution of the alcohol (1.0 eq.) in $CH_2Cl_2$ (0.2 M) was slowly added. The turbid mixture obtained was stirred at -78 $^oC$ for 2 h, after which pre-cooled $NEt_3$ (8.0 eq.)

[7.9] For acid-sensitive suspected substrates, recrystallized MCPBA was used.

was added dropwise, and the resulting mixture was allowed to warm to -30 °C over 1 h. The mixture obtained was poured at this temperature onto hexane and $CH_2Cl_2$ and gently shaken with pH 7 phosphate buffer. The layers were separated and the aqueous layer extracted with $CH_2Cl_2$. The combined organic phases were washed with aqueous 1 M $KHSO_4$, aqueous 1/3 saturated $NaHCO_3$, brine and dried ($Na_2SO_4$). Removal of the solvent under vacuum affords a residue that was either used without further purification or crudely purified in a short flash chromatography column.



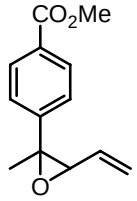

**(*Z*)-Methyl 4-(3-formyl-2-methyloxiran-2-yl)benzoate**

Following GP 4, using (crudely purified) (*Z*)-methyl 4-(3-(hydroxymethyl)-2-methyloxiran-2-yl)benzoate (**3.33**) (663 mg, 3.0 mmol, 1.0 eq.). Purification by flash chromatography (demetallated silica gel; fast elution; hexane:EtOAc, 1:1 (v:v) with 2% $Et_3N$), afforded the title compound as a pale yellow oil (343 mg, 52%).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.38; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 8.73 (dd, *J* = 0.5, 5.9 Hz, 1H), 8.00-8.05 (m, 2H), 7.48-7.53 (m, 2H), 3.90 (s, 3H), 3.44 (d, *J* = 5.9 Hz, 1H), 1.74 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 199.0, 166.6, 142.0, 130.4, 130.2, 126.5, 64.8, 64.6, 52.5, 24.7.

**General procedure for the Wittig reaction of epoxy-aldehydes to the corresponding vinyl epoxides (GP 5):**

To an ice cold slurry of methyltriphenylphosphonium bromide (1.5 eq.) in THF (0.15 M) was dropwise added a solution of KHMDS in toluene (0.5 M, 1.3 eq.). The bright yellow suspension obtained was allowed to reach room temperature and stirred for further 1½ h, after which it was re-cooled to 0 °C and a solution of the epoxy-aldehyde (1.0 eq.) in THF (0.45 M) was then added dropwise. The suspension thus obtained was allowed to reach room temperature, stirred for 1½ h further, re-cooled to ice bath temperature and filtrated through a short Celite pad to afford a tan solution. Removal of the solvent under vacuum delivered a tan solid that was triturated with $Et_2O$. The combined mother liquors were concentrated under vacuum and the obtained residue was filtrated through a short chromatography column (demetallated silica gel; fast elution; $Et_2O$). The obtained material was usually used without further purification.

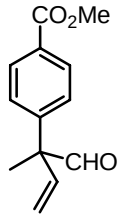



**(*Z*)-Methyl 4-(2-methyl-3-vinyloxiran-2-yl)benzoate (3.34)**

Following GP 5, using (*Z*)-methyl 4-(3-formyl-2-methyloxiran-2-yl)benzoate (343 mg, 1.55 mmol). Purification by flash chromatography (demetallated silica gel; fast elution; hexane:EtOAc, 1:1 (v:v) with 2% $Et_3N$) afforded the title compound as a yellow oil (not completely pure) (173 mg, 51%).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.54; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.92-7.97 (m, 2H), 7.34-7.39 (m, 2H), 5.39 (dd, *J* = 1.8, 15.9 Hz, 1H), 5.12 (dd, *J* = 1.8, 10.4 Hz, 1H), 5.02 (ddd, *J* = 7.9, 10.4, 15.9 Hz, 1H), 3.85 (s, 3H), 3.46 (d, *J* = 7.9 Hz, 1H), 1.64 (s, 3H).

**General procedure for the Jung rearrangement (GP 6):**
To a -78 °C cold solution of vinyl epoxide (1.0 eq.) in $CH_2Cl_2$ (0.07 M) was added $BF_3{\cdot}Et_2O$ (1.2 eq.) and the resulting solution was stirred at this temperature for 10-15 min.,[7.10] after which it was partitioned between $Et_2O$ and 1/3 saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with $Et_2O$. The combined organic phases were washed with brine, dried ($Na_2SO_4$) and concentrated. The obtained residue was purified by flash chromatography to afford the pure quaternary aldehydes.

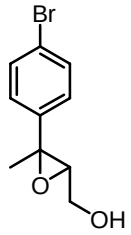



**Methyl 4-(2-methyl-1-oxobut-3-en-2-yl)benzoate (3.35)**

Following GP 6, using (*Z*)-methyl 4-(2-methyl-3-vinyloxiran-2-yl)benzoate (**3.34**) (119 mg, 0.55 mmol, 1.0 eq., not entirely pure). Purification by flash chromatography (hexane:EtOAc, 1:1 (v:v)) delivered the title compound as a yellow oil (56 mg, 47%) that was best kept frozen in a benzene matrix under argon.

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.53 (note: Rf values of the starting material and product are very similar); $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.51 (s, 1H), 7.95-8.00 (m, 2H), 7.23-7.28 (m, 2H), 6.13 (dd, *J* = 10.7, 17.6 Hz, 1H), 5.38 (d, *J* = 10.7 Hz, 1H), 5.13 (d, *J* = 17.6 Hz, 1H), 3.85 (s, 3H), 1.49 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 199.0, 166.9, 145.4, 137.9, 130.3, 129.5, 127.8, 118.4, 58.3, 52.4, 20.4; LRMS (EI) *m/z* = 218 $[M]^+$.

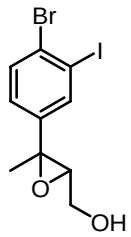
[7.10] Such long reaction time is probably not required. However, because the Rf values of both the starting vinyl epoxide and the rearranged quaternary aldehyde are very similar, the TLC plate typically has to be eluted twice which requires the time periods mentioned.



*rac*-**(3-(4-Bromophenyl)-3-methyloxiran-2-yl)methanol (3.38)**

Following GP 3, using (*E*)-3-(4-bromophenyl)but-2-en-1-ol (**3.25**) (1.0 g, 4.4 mmol). Purification by flash chromatography (short column; demetallated silica gel; fast elution; hexane:EtOAc, 1:1 (v:v)) afforded the title compound as a white solid (1.0 g, 93%).

For physical data see bellow; HPLC retention times (Rt): for the (2*R*,3*R*) enantiomer, Rt (OD-H column; hexane:$^{i}$PrOH, 9:1 (v:v); 0.6 mLmin.$^{-1}$) = 14.5 min; for the (2*S*,3*S*) enantiomer, Rt (OD-H column; hexane:$^{i}$PrOH, 9:1 (v:v); 0.6 mLmin.$^{-1}$) = 15.9 min.



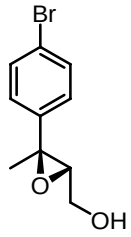
*rac*-**(3-(4-Bromo-3-iodophenyl)-3-methyloxiran-2-yl)methanol (3.39)**

Following GP 3, using (*E*)-3-(4-bromo-3-iodophenyl)but-2-en-1-ol (**3.29**) (1.0 g, 2.83 mmol). Purification by flash chromatography (short column; demetallated silica gel; fast elution; hexane:EtOAc, 1:1 (v:v)) afforded the title compound as a white solid (1.1 g, quantitative).

For physical data see bellow; HPLC retention times (Rt): for the (2*R*,3*R*) enantiomer, Rt (OD-H column; hexane:$^{i}$PrOH, 97:3 (v/v); 0.6 mLmin.$^{-1}$) = 51.7 min; for the (2*S*,3*S*) enantiomer, Rt (OD-H column; hexane:$^{i}$PrOH, 97:3 (v:v); 0.6 mLmin.$^{-1}$) = 57.7 min.

**General procedure for the Sharpless-Katsuki asymmetric epoxidation (GP 7):**
To a -25 $^{o}$C cold suspension of powder 4Å molecular sieves (55 mg per mmol of the allylic alcohol) in $CH_2Cl_2$ (0.16 M with respect to the allylic alcohol) was dropwise added a solution of L-(+)-diethyl tartrate (7.5 mol%) in $CH_2Cl_2$ (1.1 M), followed by $Ti(O^{i}Pr)_4$ (5 mol%) and finally a solution of freshly prepared $^{t}$BuOOH in toluene (3.8 M, 2.0 eq.) with 5 min. intervals between additions. After aging for 1½ h at -25 $^{o}$C, a solution of the allylic alcohol (1.0 eq.) in $CH_2Cl_2$ (1.29 M) was added dropwise, over 20 min., and the resulting suspension stirred for further 4 h at this temperature. The reaction was quenched at -25 $^{o}$C by addition of an aqueous 10% NaOH in brine solution (0.1 mL per mmol of the allylic alcohol) followed by $Et_2O$ (0.6 mL per mmol of allylic alcohol). After stirring at -25 $^{o}$C for 5 min., this suspension was allowed to reach 5 $^{o}$C over 10 min. and then $MgSO_4$ (79.5 mg per mmol of allylic alcohol) and Celite (10.5 mg per mmol of the allylic alcohol) were simultaneously added. After stirring at room temperature for 10 min., the suspension was filtrated through a short

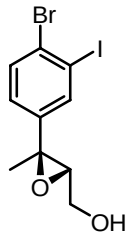
pad of Celite, and the filtrate was concentrated under vacuum to afford a turbid pale yellow oil which was then taken up in toluene (2 times) and concentrated under vacuum affording the crude epoxide which, if necessary, was further purified by recrystallization.




**((2*S*,3*S*)-3-(4-Bromophenyl)-3-methyloxiran-2-yl)methanol (3.38)**

Following GP 7, using (*E*)-3-(4-bromophenyl)but-2-en-1-ol (**3.25**) (5.0 g, 22.0 mmol). The crude product was obtained as a pale yellow solid (4.7 g, 88%, 83% *ee*). Re-crystallization from hot hexane: $Et_2O$, 2:1 (v:v) (approximately 500 mL) afforded the title compound as white needles (4.1 g, 76%, 96-98% *ee*).

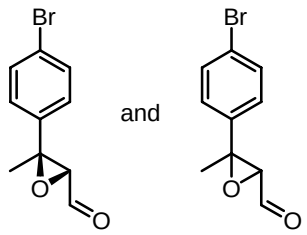
$R_f$ (hexane:EtOAc, 1:1 (v:v); double elution) 0.42; mp 130-132 $^oC$; $^1H$-NMR ($CDCl_3$, 300 MHz) δ 7.38-7.42 (m, 2H), 7.13-7.17 (m, 2H), 3.90 (dd, *J* = 4.4, 12.2 Hz, 1H), 3.77 (dd, *J* = 6.4, 12.2 Hz, 1H), 2.98, (dd, *J* = 4.4, 6.4 Hz, 1H), 1.65 (brs, 1H), 1.61 (s, 3H); $^{13}C$-NMR ($CDCl_3$, 75 MHz) δ 141.3, 131.7, 127.1, 121.8, 66.2, 61.5, 60.6, 17.9; LRMS (EI) *m/z* = 243 $[M]^+$; $[\alpha]_D^{25}$ -9.20 (*c* 1.8, $CHCl_3$); Anal. Calcd. for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56. Found: C, 49.30; H, 4.39.




**((2*S*,3*S*)-3-(4-Bromo-3-iodophenyl)-3-methyloxiran-2-yl) methanol (3.39)**

Following GP 7, using (*E*)-3-(4-bromo-3-iodophenyl)but-2-en-1-ol (**3.29**) (2.8 g, 7.93 mmol). The crude product was obtained as white solid (2.91 g, quantitative, 92-94% *ee*) which typically was used without further purification. If desired, it can be recrystallized from hot hexane: $Et_2O$, 2:1 (v:v) (approximately 300 mL) affording the title compound as white needles (2.6 g, 91%, >99% *ee*).

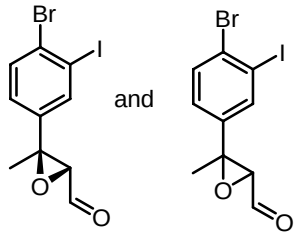
$R_f$ (hexane:EtOAc, 1:1 (v:v); double elution) 0.50; mp 59-61 $^oC$; $^1H$-NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.11 (dd, *J* = 2.1, 8.3 Hz, 1H), 3.88 (dd, *J* = 4.4, 12.2 Hz, 1H), 3.75 (dd, *J* = 6.3, 12.2 Hz, 1H), 2.96 (dd, *J* = 4.4, 6.3, 1H), 1.93 (bs, 1H), 1.59 (s, 3H); $^{13}C$-NMR ($CDCl_3$, 75 MHz) δ 143.1, 137.2, 132.7, 129.0, 126.7, 101.5, 66.1, 61.3, 59.9, 17.7; LRMS (EI) *m/z* = 368 $[M]^+$; $[\alpha]_D^{25}$ -9.2 (*c* 2.2, $CHCl_3$); Anal. Calcd. for $C_{10}H_{10}BrIO_2$: C, 32.55; H, 2.73. Found: C, 32.61; H, 2.67.




**(2*R*,3*S*)-3-(4-Bromophenyl)-3-methyloxirane-2-carbaldehyde**
and
***rac*-3-(4-Bromophenyl)-3-methyloxirane-2-carbaldehyde**

Following GP 4, using (2*R*,3*S*)-3-(4-bromophenyl)-3-methyloxirane-2-carbaldehyde (**3.38**) (2.1 g, 8.6 mmol). The residue obtained from work up was crudely purified *via* a short chromatography column filtration (demetallated silica gel; fast elution; hexane:EtOAc, 1:1 (v:v)) to afford a pale thick yellow oil that crystallized upon standing in the cold (2.0g) and was used without further purification.

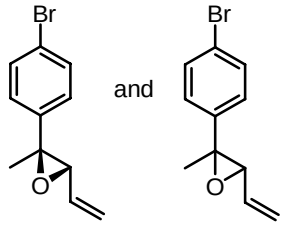
$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.52; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.55 (d, $J$ = 4.9 Hz, 1H), 7.46-7.50 (m, 2H), 7.19-7.23 (m, 2H), 3.27 (d, $J$ = 4.9 Hz, 1H), 1.80 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 197.6, 139.4, 132.0, 127.1, 122.7, 66.6, 63.2, 18.1.




**(2*R*,3*S*)-3-(4-Bromo-3-iodophneyl)-3-methyloxirane-2-carbaldehyde**
and
***rac*-3-(4-Bromo-3-iodophneyl)-3-methyloxirane-2-carbaldehyde**

Following GP 4, using ((2*S*,3*S*)-3-(4-bromo-3-iodophenyl)-3-methyloxiran-2-yl)methanol (**3.39**) (3.76 g, 10.19 mmol). The residue obtained from work up was crudely purified *via* a short chromatography column filtration (demetallated silica gel; fast elution; hexane:EtOAc, 1:1 (v:v)) to afford a pale thick yellow oil that crystallized upon standing in the cold (3.40 g) and was used without further purification.

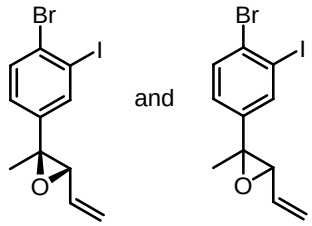
$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.57; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.64, (d, $J$ = 4.0 Hz, 1H), 7.96 (d, $J$ = 2.2 Hz, 1H), 7.73 (d, $J$ = 8.3 Hz, 1H), 7.40 (dd, $J$ = 2.2, 8.3 Hz, 1H), 3.48 (d, $J$ = 4.0, 1H), 1.82 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 205.6, 142.2, 137.5, 132.9, 129.2, 127.3, 101.1, 66.2, 62.0, 16.9; LRMS (EI) $m/z$ = 366 $[M]^+$.




**(2*R*,3*S*)-3-(4-Bromophenyl)-2-methyl-3-vinyloxirane (3.40)**
and
***rac*-3-(4-Bromo-3-phenyl)-2-methyl-3vinyloxirane (3.40)**

Following GP 5 using (2*R*,3*S*)-3-(4-bromophenyl)-3-methyloxirane-2-carbaldehyde (2.0 g crudely purified, 8.3 mmol). The residue obtained from work up was crudely purified in a short chromatography column (demetallated silica gel; fast elution; $Et_2O$). The yellow oil obtained was used without further purification (2.0 g).

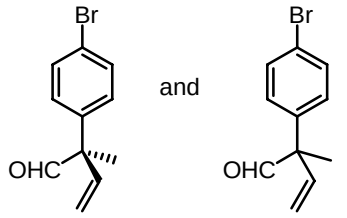
$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.57; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.44-7.48 (m, 2H), 7.21-7.26 (m, 2H), 5.84 (ddd, *J* = 7.1, 10.4, 17.4 Hz, 1H), 5.50 (d, *J* = 17.4 Hz, 1H), 5.42 (d, *J* = 10.4 Hz, 1H), 3.26 (d, *J* = 7.1 Hz, 1H), 1.64 (s, 3H);$^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 141.6, 132.8, 131.7, 127.1, 121.6, 121.3, 67.1, 62.1, 17.6.




**(2*R*,3*S*)-3-(4-bromo-3-iodophenyl)-2-methyl-3-vinyl oxirane (3.41)**
and
***rac*-3-(4-bromo-3-iodophenyl)-2-methyl-3-vinyloxirane (3.41)**

Following GP 5, using (2*R*,3*S*)-3-(4-bromo-3-iodophenyl)-3-methyloxirane-2-carbaldehyde (3.33 g crudely purified, 9.1 mmol). The residue obtained from work up was crudely purified in a short chromatography column (demetallated silica gel; fast elution; $Et_2O$). The yellow oil obtained was used without further purification (2.97 g).

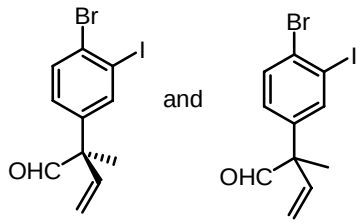
$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.60; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, *J* = 2.2 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.19 (dd, *J* = 2.2, 8.3 Hz, 1H), 5.82 (sept., *J* = 7.0, 10.5, 17.3 Hz, 1H), 5.51 (ddd, *J* = 0.9, 1.4, 17.3 Hz, 1H), 5.44 (ddd, *J* = 0.8, 1.4, 10.5 Hz, 1H), 3.24 (d, *J* = 7.0 Hz, 1H), 1.62 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 143.4, 137.2, 133.8, 132.7, 132.5, 126.7, 121.7, 121.7, 101.5, 67.0, 61.3, 17.5; LRMS (EI) *m/z* =364 $[M]^+$.




**(*R*)-2-(4-Bromophenyl)-2-methylbut-3-enal (3.42)**
and
***rac*-2-(4-Bromophenyl)-2-methylbut-3-enal (3.42)**

Following GP 6, using (2*R*,3*S*)-3-(4-bromophenyl)-2-methyl-3-vinyloxirane (**3.40**) (2.0 g crudely purified, 8.3 mmol). Purification by flash chromatography (hexane: $Et_2O$, 5:1 (v:v)) delivered the title compound as a pale yellow oil (1.19 g, 58% based on allylic alcohol (**3.38**)) that was best kept frozen in a benzene matrix under argon.

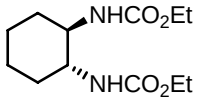
$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.52; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.54 (s, 1H), 7.48-7.53 (m, 2H), 7.09-7.14 (m, 2H), 6.16 (dd, *J* = 10.8, 17.6 Hz, 1H), 5.43 (d, *J* = 10.8 Hz, 1H), 5.18 (d, *J* = 17.6 Hz, 1H), 1.52 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 199.0, 139.2, 138.0, 132.2, 129.5, 121.9, 118.2, 57.7, 20.4; $[\alpha]_D^{25}$ +47.4 (*c* 2.0, $CHCl_3$); Anal. Calcd. for $C_{11}H_{11}BrO$: C, 55.25; H, 4.64. Found: C, 55.25; H, 4.50.




**(*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-enal (3.43)**
and
***rac*-2-(4-bromo-3-iodophenyl)-2-methylbut-3-enal (3.43)**

Following GP 6, using (2*R*,3*S*)-3(4-bromo-3-iodophenyl)-2-methyl-3-vinyloxirane (**3.41**) (2.81 g crudely purified, 7.70 mmol, 1.0 eq.). Purification by flash chromatography (hexane: $Et_2O$, 3:1 (v:v)) delivered the title compound as a pale yellow oil (1.9 g, 52% based on allylic alcohol (**3.39**)) that was best kept frozen in a benzene matrix under argon.

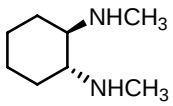
$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.47; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.52, (s, 1H), 7.71 (d, *J* = 2.2 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.07 (ddd, *J* = 0.4, 2.2, 8.3, Hz, 1H), 6.12 (ddd, *J* = 0.40, 10.7, 17.6 Hz, 1H), 5.46 (d, *J* = 10.7, 1H), 5.20 (d, *J* = 17.6, 1H), 1.51 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 198.5 141.1, 139.5, 137.4, 133.1, 129.2, 129.0, 118.7, 102.2, 57.4, 20.4; LRMS (EI) *m/z* = 337 $[M\text{-}C_2H_3]^+$; $[\alpha]_D^{25}$ +27.8 (*c* 1.3, $CHCl_3$).




**(*R*,*R*)-(2-Ethoxycarbonylaminocyclohexyl)carbamic acid ethyl ester**

Following a literature procedure,[7.11] to an ice cold solution of (*R*,*R*)-cyclohexane-1,2-diamine (2.8 g, 24.5 mmol, 1.0 eq.) in toluene (41 mL), were simultaneously added freshly distilled ethyl chloroformate (5.78 mL, 60.4 mmol, 2.4 eq.) and a solution of NaOH (62.4 mmol 2.5 eq.) in water (2.6 mL) through two syringes. The addition rate was such as to keep the internal temperature bellow 10 $^{o}$C. The thick suspension thus obtained was allowed to reach room temperature and stirred for 4 h further, after which the heavy precipitate was filtrated off and rinsed with $CH_2Cl_2$ (15 mL). The filtrate was dried ($Na_2SO_4$) and the solvent removed under vacuum to afford a light pinkish solid residue, which was recrystallized from $CH_2Cl_2$ (approximately 90 mL) to which a minimum amount of pentane was carefully added (8-10 Pasteur pipettes). The title compound was obtained as a white solid (5.3 g, 84%).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.35; mp 165-167 $^{o}$C (lit. 166-167 $^{o}$C); $^{1}$H-NMR ($CDCl_3$, 300 MHz) δ 4.99 (brs, 2H), 4.06 (q, *J* = 7.0 Hz, 4H), 3.26-3.38 (m, 2H), 1.98-2.06 (m, 2H), 1.67-1.75 (m, 2H), 1.16-1.26 (m, 10H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 158.4, 62.1, 56.6, 34.2, 26.1, 15.9; $[\alpha]_D^{25}$ +45.4 (*c* 1.0, $CHCl_3$) (lit. $[\alpha]_D^{25}$ +45.6 (*c* 1.05, $CHCl_3$).



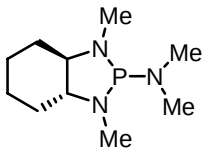

**(*R*,*R*)-1,2-*N*,*N*´-(dimethyl)aminocyclohexane**

Following a literature procedure,[7.11] to a stirred ice cold suspension of $LiAlH_4$ (3.1 g, 82.0 mmol, 4.0 eq.) in THF (108 mL) was portionwise added (*R*,*R*)-(2-ethoxycarbonylaminocyclohexyl)carbamic acid ethyl ester (5.3 g, 20.5 mmol, 1.0 eq.). The suspension was stirred at ice bath temperature for 15 min., refluxed for 36 h, after which it was re-cooled to 0 $^{o}$C and ethylenediamine (7.1 mL) was slowly added (gas evolution) followed by an aqueous 15% NaOH solution (3.4 mL) and finally water (7.0 mL), with 3 min intervals between additions. The obtained suspension was stirred at room temperature for 5 min., filtered through a pad of Celite and the precipitate rinsed with $Et_2O$ (120 mL). The filtrate was dried ($Na_2SO_4$), concentrated under vacuum, affording a pale yellow

[7.11] (a) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224. (b) Alexakis, A.; Chauvin, A.-S.; Stouvenel, R.; Vrancken, E.; Mutti, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *12*, 1171. (c) Alexakis, A.; Mutti, S.; Normant, J. F.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 437.

oil residue which was purified by bulb-to-bulb distillation at reduced pressure (20-22 mmHg; oven temperature: 90-95 °C). The title compound was obtained as a colorless oil, which crystallized upon cooling (2.3 g, 80%).

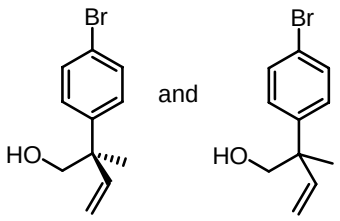
$R_f$ ($^i$PrOH: aqueous 25% ammonia, 7:3 (v:v)) 0.55; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 6H), 1.98-2.11 (m, 4H), 1.67-1.73 (m, 2H), 1.56 (brs, 2H), 1.16-1.24 (m, 2H), 0.87-0.98 (m, 2H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 63.5, 33.9, 31.0, 25.2; $[\alpha]_D^{25}$ -144.8 (*c* 4.45, $CHCl_3$) (lit. $[\alpha]_D^{25}$ -145.7 (*c* 4.47, $CHCl_3$)).




**Alexis reagent (3.44)**

Following a literature procedure,[7.11] (*R*,*R*)-1,2-*N*,*N*′-(dimethyl)aminocyclohexane (1.5 g, 10.5 mmol, 1.0 eq.) and hexamethylphosphorous triamide (2.39 mL, 13.2 mmol, 1.25 eq.) were heated neat under argon at 150 °C for 96 h (gas evolution) during which period a black precipitate formed. A stream of argon was passed occasionally through the reaction flask to remove the dimethyamine being formed. The obtained tanned suspension was allowed to reach room temperature under argon without stirring and the supernatant solution was carefully decanted off and bulb-to-bulb distilled under reduced pressure (0.5-0.7 mm Hg; oven temperature: 80-85 °C) delivering the desired diazaphospholidine (**3.44**) as a colorless oil (1.8 g, 80%) which was stored as a 0.2 M solution in benzene and kept under argon in the refrigerator.

$^{31}$P-NMR ($C_6D_6$, 202 MHz) δ 123.15; $^1$H-NMR ($C_6D_6$, 300 MHz) δ 2.11-2.66 (m, 14H), 1.78-1.88 (m, 2H), 1.47-1.61 (m, 2H), 0.78-1.15 (m, 4H); $^{13}$C-NMR ($C_6D_6$, 75 MHz) δ 68.8 (d, $J_{CP}$ = 3.5 Hz), 66.7 (d, $J_{CP}$ = 9.1 Hz), 38.0 (d, $J_{CP}$ =17.6 Hz), 33.9 (s), 33.4 (s), 29.9, 29.6, 24.6, 24.2; $[\alpha]_D^{25}$ -100.1° (*c* 2.7, $C_6H_6$) (lit. $[\alpha]_D^{25}$ -100.4° (*c* 2.7, $C_6H_6$).

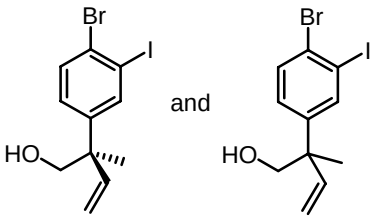



**(*R*)-2-(4-Bromophenyl)-2-methylbut-3-en-1-ol (3.45)**
and
***rac*-2-(4-Bromo-3-iodophenyl)-2-methylbut-3-en-1-ol (3.45)**

A solution of (*R*)-2-(4-bromophenyl)-2-methylbut-3-enal (**3.42**) (1.28 g, 5.35 mmol, 1.0 eq.) in MeOH (62 mL) at 0 °C was treated with $NaBH_4$ (181 mg, 4.76 mmol, 0.9 eq.). After stirring for 15 min. at ice bath

temperature, the solution was allowed to warm to room temperature and stirred for further 2 h, at which time it was concentrated to ½ of its initial volume and partitioned between water (15 mL) and $Et_2O$ (120 mL). The aqueous layer was extracted with $Et_2O$ (20 mL) and EtOAc (20 mL) and the combined organic phases were washed with brine (10 mL), dried ($NaSO_4$) and concentrated under vacuum to afford a yellow oil residue which typically was used without further purification. For analytical purposes, the crude product was purified by flash chromatography on silica gel (hexane:EtOAc, 1:1 (v:v)) (1.0 g, 78%).

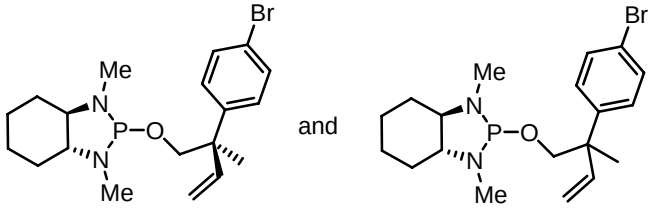
$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.53; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.43-7.47 (m, 2H), 7.20-7.25 (m, 2H), 6.02 (dd, *J* = 10.8, 17.6 Hz, 1H), 5.28 (dd, *J* = 0.9, 10.8 Hz, 1H), 5.13 (dd, *J* = 0.9, 17.6 Hz, 1H), 3.76 (s, 2H), 1.40 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 143.8, 143.2, 131.7, 129.1, 120.7, 115.4, 69.9, 47.0, 22.9; LRMS (EI) *m/z* = 242 $[M]^+$.




**(*R*)-2-(4-Bromo-3-iodophenyl)-2-methylbut-3-en-1-ol (3.46)**
and
***rac*-2-(4-Bromo-3-iodophenyl)-2-methylbut-3-en-1-ol (3.46)**

A solution of (*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-enal (**3.43**) (1.18 g, 3.23 mmol, 1.0 eq.) in MeOH (35 mL) at 0 °C was treated with $NaBH_4$ (114 mg, 3.0 mmol, 0.9 eq.). After stirring for 15 min. at ice bath temperature, the solution was allowed to warm to room temperature and stirred for further 2 h, at which time it was concentrated to ½ of its initial volume and partitioned between water (15 mL) and $Et_2O$ (50 mL). The aqueous layer was extracted with $Et_2O$ (20 mL) and EtOAc (20 mL) and the combined organic phases were washed with brine (10 mL), dried ($NaSO_4$) and concentrated under vacuum to afford a yellow oil residue which typically was used without further purification. For analytical purposes the crude product was purified by flash chromatography on silica gel (hexane:EtOAc, 1:1 (v:v)) (960 mg, 81%).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.52; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, *J* = 2.3 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.20 (dd, *J* = 2.3, 8.4 Hz, 1H), 5.98 (dd, *J* = 10.8, 17.6 Hz, 1H), 5.30 (dd, *J* = 0.9, 10.8, 2H), 5.14 (dd, *J* = 0.9, 17.6, 1H), 3.74 (s, 2H), 1.38 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 145.9, 142.6, 139.3, 132.6, 128.7, 127.9, 115.9, 101.7, 69.7, 46.8, 22.9; LRMS (EI) *m/z* = 368 $[M]^+$.

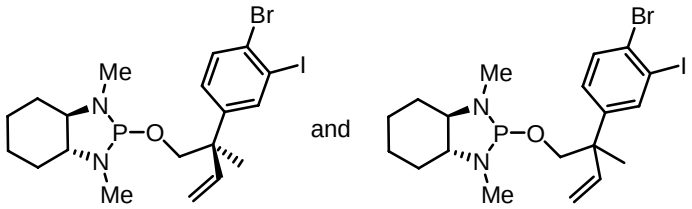



**Determination of the *ee* of alcohol (3.45) using the Alexis reagent (3.44)**

To the Alexis reagent (**3.44**) (0.58 mL of a 0.2 M solution in benzene, 0.12 mmol, 1.1 eq.) was added a solution of (*R*)-2-(4-bromophenyl)-2-methylbut-3-en-1-ol (**3.45**) (25 mg, 0.10 mmol, 1.0 eq.) in benzene (0.2 mL). After stirring at room temperature under argon for 15 h, the resulting solution was then transferred into an NMR tube and $C_6D_6$ (100 µl) was added for locking.

For ***rac*-(3.47)**: $^{31}$P-NMR ($C_6D_6$, 202 MHz) δ 138.9 and 138.7 (equal intensities).

For **(3.47)**: $^{31}$P-NMR ($C_6D_6$, 202 MHz) δ 138.7.

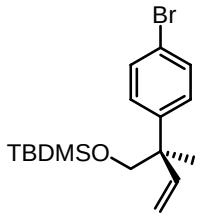



**Determination the *ee* of alcohol (3.46) using the Alexis reagent (3.44)**

To the Alexis reagent (**3.44**) (0.10 mL of a 0.2 M solution in benzene, 0.02 mmol, 1.1 eq.) was added a solution of (*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-en-1-ol (**3.46**) (7.0 mg, 0.018 mmol, 1.0 eq.) in benzene (0.2 mL) and the resulting solution was left stirring at room temperature under argon over 15 h. After stirring at room temperature under argon for 15 h, the resulting solution was then transferred into an NMR tube and $C_6D_6$ (100 µl) was added for locking.

For **rac-(3.48)**: $^{31}$P-NMR ($C_6D_6$, 202 MHz) δ 139.0 and 138.8 (equal intensities).

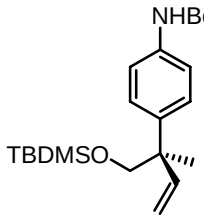
For **(3.48)**: $^{31}$P-NMR ($C_6D_6$, 202 MHz) δ 138.8.




**(*R*)-(2-(4-Bromophenyl)-2methylbut-3-enyloxy)(*tert*-butyl) dimethylsilane (3.49)**

To a solution of TBDMSCl (1.11 g, 7.34 mmol, 1.5 eq.) and imidazole (900 mg, 13.2 mmol, 2.7 eq.) in DMF (5.3 mL) was added a solution of (crude) (*R*)-2-(4-bromophenyl)-2-methylbut-3-en-1-ol (**3.45**) (1.18 g, 4.9 mmol, 1.0 eq.) in DMF (7.5 mL). After stirring at room temperature overnight, the resulting solution was partitioned between aqueous 1 M HCl (75 mL) and $Et_2O$ (150 mL). The aqueous layer was extracted with $Et_2O$ (2 portions of 30 mL) and the combined organic phases were washed with ½ saturated $NaHCO_3$ (100 mL), brine (50 mL) and dried ($Na_2SO_4$). Removal of the solvent under vacuum afforded a yellow oil residue that was purified by flash chromatography on silica gel (hexane:$Et_2O$, 5:1 (v:v)). The title compound was obtained as a pale yellow oil (1.6 g, 79% based on quaternary aldehyde (**3.42**)).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.80; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.43-7.48 (m, 2H), 7.26-7.31 (m, 2H), 6.10 (dd, *J* = 10.9, 17.7 Hz, 1H), 5.20 (dd, *J* = 1.2, 10.9 Hz, 1H), 5.10 (dd, *J* = 1.2, 17.7 Hz, 1H), 3.76 (d, *J* = 12.3 Hz, 1H), 3.72 (d, *J* = 12.3 Hz, 1H), 1.42, (s, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 150.3, 149.5, 136.4, 134.8, 125.5, 119.2, 76.0, 52.1, 31.4, 28.2, 23.8, 0.03; $[\alpha]_D^{25}$ -9.95 (*c* 2.0, $CHCl_3$).

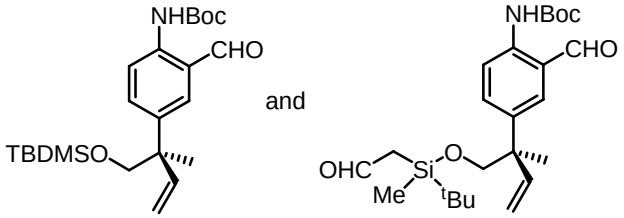



**(*R*)-*tert*-Butyl 4-(1-(*tert*-butyldimethylsilyloxy)-2-methylbut-3-en-2-yl)phenylcarbamate (3.50)**

A reddish suspension of (*R*)-(2-(4-bromophenyl)-2-methylbut-3-enyloxy)(*tert*-butyl)dimethylsilane (**3.49**) (975 mg, 2.74 mmol, 1.0 eq.), $Pd_2(dba)_3.CHCl_3$ complex (117 mg, 0.11 mmol, 4 mol%), $^tBu_3P$ (56 mg, 0.27 mmol, 9.8 mol%), freshly prepared NaOPh (491 mg, 4.23 mmol, 1.5 eq.) (for the preparation of NaOPh see section 7.2) and *tert*-butylcarbamate (495 mg, 4.23 mmol, 1.5 eq.) in toluene (8.5 mL) was stirred at 100 $^oC$ for ½ h, during which period a tan color developed. The solvent was then removed under vacuum and the dark tan residue obtained was purified by flash chromatography on silica gel (hexane: $Et_2O$, 3:1 (v:v) with 0.5% $Et_3N$) delivering the title compound as a yellow oil (880 mg, 82%).

$R_f$ (hexane:$Et_2O$, 3:1 (v:v)) 0.53; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, 4H), 6.48 (brs, 1H), 6.10 (dd, *J* = 10.8, 17.6 Hz, 1H), 5.16 (dd, *J* = 1.2, 10.8 Hz, 1H), 5.08 (dd, *J*

= 1.2, 17.6 Hz, 1H), 3.76 (d, *J* = 9.6 Hz, 1H), 3.70 (d, *J* = 9.6 Hz, 1H), 1.56 (s, 9H), 1.41 (s, 3H), 0.89 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 158.4, 150.1, 145.8, 141.8, 133.4, 123.6, 118.7, 85.9, 76.1, 51.8, 33.9, 31.4, 28.2, 23.8, 0.0; LRMS (EI) *m/z* = 391 $[M]^+$; $[\alpha]_D^{25}$ -10.2 (*c* 2.0, $CHCl_3$); Anal. Calcd. for $C_{22}H_{37}NO_3Si$: C, 67.47; H, 9.52; N, 3.58. Found: C, 67.74; H, 9.54; N, 3.30.

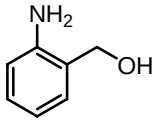



**(*R*)-*tert*-Butyl 4-(2-((tert-butyl dimethylsilyloxy)methyl)but-3-en-2-yl)-2-formylphenylcarbamate (3.51)**
and
***tert*-Butyl 4-((*R*)-2-(*tert*-butyl(methyl (2-oxoethyl)silyloxy)but-3-en-2-yl)-2-formylphenylcarbamate (3.55)**

To a solution of (*R*)-*tert*-butyl 4-(1-(*tert*-butyldimethylsilyloxy)-2-methylbut-3-en-2-yl)phenylcarbamate (**3.50**) (663 mg, 1.69 mmol, 1.0 eq.) in $Et_2O$ (5.1 mL) at -78 °C was dropwise added, over 5 min., a solution of $^t$BuLi in pentane (1.7 M, 5.6 mL, 9.5 mmol, 5.5 eq.) The dark mixture obtained was stirred at -78 °C for 15 min., after which the temperature was increase to -25 °C (a cooling bath at this temperature was inserted) and stirring continued for 4 h further, during which period the temperature was slowly allowed to rise to -15 °C. The mixture was then re-cooled to -78 °C and DMF (1.57 mL, 20.3 mmol, 12 eq.) was added in a dropwise manner. After stirring at -78 °C for 25 min., the temperature was increase to -25 °C (a cooling bath at this temperature was inserted) stirring continued for 2 h further, during which period the temperature was allowed to slowly reach -10 °C. The turbid mixture obtained was partitioned between a solution of aqueous 5% HCl:½ brine (1:1 (v:v)) (50 mL) and $Et_2O$ (90 mL). The aqueous layer was extracted with $Et_2O$ (2 portions of 30 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum to afford a yellowish oil residue. Purification by flash chromatography on silica gel (hexane: $Et_2O$, 3:1 (v:v)) delivered (*R*)-*tert*-butyl 4-(2-((tert-butyl dimethylsilyloxy)methyl)but-3-en-2-yl)-2-formylphenylcarbamate (**3.51**) as a viscous yellow oil (418 mg, 59%) and *tert*-butyl 4-((*R*)-2-(*tert*-butyl (methyl) (2-oxoethyl)silyloxy)but-3-en-2-yl)-2-formylphenylcarbamate (**3.55**) as a viscous yellow oil (166 mg, 22%).

For (*R*)-*tert*-butyl 4-(2-((tert-butyl dimethylsilyloxy)methyl)but-3-en-2-yl)-2-formylphenylcarbamate (**3.51**): $R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.63; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.36 (brs, 1H), 9.91 (s, 1H), 8.40 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 2.2 Hz, 1H), 7.61 (dd, *J* = 2.2, 8.8 Hz, 1H), 6.10 (dd, *J* = 10.9, 17.7 Hz, 1H), 5.22 (d, *J* = 10.9 Hz, 1H), 5.10 (d, *J* = 17.7 Hz, 1H), 3.76 (s, 2H), 1.57 (s, 9H), 1.43 (s, 3H), 0.87 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 200.9, 158.6, 149.3, 145.3, 144.5, 140.8, 140.7, 126.4, 123.4, 119.5, 86.4, 75.8, 51.7, 33.9, 31.4, 28.3, 23.8, 0.0. LRMS (EI) *m/z* = 419 [$M^+$]; $[\alpha]_D^{25}$ -11.9 (*c* 2.3, $CHCl_3$); Anal. Calcd. for $C_{23}H_{37}NO_4Si$: C, 65.83; H, 8.89; N, 3.34. Found: C, 65.99; H, 8.62; N, 3.12.

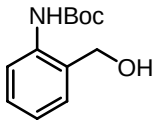
For *tert*-butyl 4-((*R*)-2-(*tert*-butyl (methyl) (2-oxoethyl)silyloxy)but-3-en-2-yl)-2-formylphenylcarbamate (**3.55**): $R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.22; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.22 (s, 1H), 9.78 (s, 1H), (9.54 (t, *J* = 4.3 Hz, corresponding to one of the diastereomers, partial overlap with t at δ = 9.52 ppm) and 9.52 (t, *J* = 4.3 Hz, corresponding to the other diastereomer, partial overlap with t at δ = 9.54 ppm), 1H), 8.27 (d, *J* = 8.9 Hz, 1H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.44 (dd, *J* = 2.3, 8.9 Hz, 1H), 5.93 (dd, *J* = 10.8, 17.6 Hz, 1H), (4.97 (dd, *J* = 1.1, 10.8 Hz, corresponding to one of the diastereomers, partial overlap with dd at δ = 4.96 ppm) and 4.96 (dd, *J* = 1.1, 10.8 Hz, corresponding the other diastereomers, partial overlap with dd at δ = 4.97 ppm), 1H), (5.11 (dd, *J* = 1.1, 17.6 Hz, corresponding to one of the diastereomers, partial overlap with dd at δ = 5.10 ppm) and 5.10 (dd, *J* = 1.1, 17.6 Hz, corresponding to the other diastereomer, partial overlap with dd at δ = 5.11 ppm), 1H), (3.70 (d, *J* = 9.7 Hz, corresponding to one of the diastereomers, partial overlap with d at δ = 3.69 ppm) and 3.69 (d, *J* = 9.7 Hz, corresponding to the other diastereomers, partial overlap with d at δ = 3.70 ppm), 1H), (3.68 (d, *J* = 9.7 Hz, corresponding to one of the diastereomers, partial overlap with d at δ = 3.67 ppm) and 3.67 (d, *J* = 9.7 Hz, corresponding to the other diastereomers, partial overlap with d at δ = 3.68 ppm), 1H), (2.26 (dd, *J* = 4.3, 10.5 Hz, corresponding to one of the diastereomers, partial overlap with dd at δ = 2.25 ppm) and 2.25 (dd, *J* = 4.3, 10.5 Hz, corresponding to the other diastereomers, partial overlap with dd at δ = 2.26 ppm), 1H), (2.14 (dd, *J* = 4.3, 10.5 Hz, corresponding to one of the diastereomers, partial overlap with dd at δ = 2.12 ppm) and 2.12 (dd, *J* = 4.3, 10.5 Hz, corresponding to the other diastereomer, partial overlap with dd at δ = 2.14 ppm), 1H), 1.43 (s, 9H), (0.77 (s) and 0.76 (s), 1H), (0.01 (s) and 0.00 (s), 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 200.1, 195.5, 153.2, 143.4, 140.2, 138.5, 135.2, 135.1, 121.1, 118.2, 114.6, 81.1, 71.1, 46.3, 36.8, 28.5, 25.8, 22.8, 19.2, -6.3; LRMS (EI) *m/z* = 447 [$M]^+$; Anal. Calcd. for $C_{24}H_{37}NO_5Si$: C, 64.39; H, 8.33; N, 3.13. Found: C, 64.13; H, 8.03; N, 2.95.



**2-Aminobenzyl alcohol (3.60)**

Following a literature procedure,[7.12] a one-liter three-necked-flask was equipped with an efficient magnetic stirrer bar, a solid Soxhlet extractor and an efficient reflux condenser, with the extractor inserted between the flask and the reflux condenser. A suspension of $LiAlH_4$ (10.0 g, 0.26 mol, 2.35 eq.) in $Et_2O$ (620 mL) was placed in the flask and anthranilic acid (15.4 g, 0.12 mol, 1.0 eq.) was placed in the extractor thimble. The suspension was refluxed until all the anthranilic acid has been transferred to the reaction flask (6½ h) (caution: the first discharges from the extractor into the reaction flask proceed with substantial gas evolution). The obtained suspension was then cooled to ice bath temperature and excess of hydride was decomposed by slow addition of iced water (10 mL), followed by aqueous 15% NaOH (10 mL) and finally water (30 mL). After stirring at 0 °C for 15 min., the granular suspension obtained was filtered and the filtrate was washed with an aqueous 10% NaOH solution (200 mL). The resulting aqueous layer was extracted with $Et_2O$ (2 portions of 100 mL); the combined organic phases were washed with brine (50 mL) and dried ($Na_2SO_4$). Removal of the solvent under vacuum delivered the title compound as a pale yellow solid (12.2 g, 88%) which was used without further purification.

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.22; mp 81-83 °C (lit.: 82 °C); $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.14 (´t´d, *J* = 1.6, 7.7, 7.7 Hz, 1H), 7.07 (dd, *J* = 1.6, 7.9 Hz, 1H), 6.70-6-76 (m, 2H), 4.67 (s, 2H), 3.30 (brs, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 146.1, 129.6, 129.4, 125.1, 118.5, 116.3, 64.5.

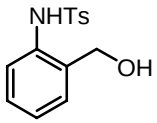


***tert*-Butyl 2-(hydroxymethyl)phenylcarbamate (3.61a)**

Following a literature procedure,[7.13] a solution of 2-aminobenzyl alcohol (**3.60**) (2.0 g, 16.3 mmol, 1.0 eq.) and $Boc_2O$ (5.3 g, 24.3 mmol, 1.5 eq.) in THF (45 mL) was stirred at room temperature for 62 h, after which the solvent was removed under vacuum affording a deep tanned oil residue. Purification by flash chromatography on silica gel (hexane: $Et_2O$, 1:1 (v:v)) afforded the title compound as a yellow oil (5.6 g, quantitative), which was used without further purification.

[7.12] Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 2548.
[7.13] Nugent, B. M.; Williams, A. L.; Prabhakaran, E. N.; Johnston, J. N. *Tetrahedron* **2003**, *59*, 8877.

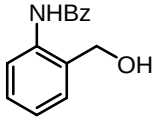
$^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.72 (brs, 1H), 7.29 (ddd, *J* = 8.7, 8.7, 1.3 Hz, 1H), 7.13 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.00 (ddd, *J* = 7.4, 7.4, 0.8 Hz, 1H), 4.61 (d, *J* = 2.8 Hz, 2H), 2.90 (brs, 1H), 1.52 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 153.8, 138.1, 129.5, 129.1, 123.4, 121.4, 80.7, 64.3, 28.6.




**_N_-(2-(Hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (3.61b)**

Following a literature procedure,[7.14] a solution of TsCl (9.65 g, 50.6 mmol, 1.1 eq.) in $CHCl_3$ (47 mL) was dropwise added over 40 min. to a solution of 2-aminobenzyl alcohol (**3.60**) (5.61 g, 45.6 mmol, 1.0 eq.) and pyridine (4.4 mL, 54.7 mmol, 1.2 eq.) in $CHCl_3$ (168 mL) at room temperature. The deep yellow solution obtained was stirred at room temperature overnight, after which it was concentrated under vacuum to a golden thick oil which was then partitioned between EtOAc (100 mL) and aqueous saturated $NH_4Cl$ (80 mL). The aqueous layer was extracted with EtOAc (50 mL) and the combined organic phases were washed with brine (30 mL) and dried ($Na_2SO_4$). Removal of the solvent under vacuum afforded the title compound as a beige solid (11.8 g, 93%) which was used without further purification.

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.35; mp 143-146 $^o$C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.90 (brs, 1H), 7.61-7.66 (m, 2H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.19-7.28 (m, 3H), 7.07-7.09 (m, 2H), 4.38 (s, 2H), 2.38 (s, 3H), 2.08 (brs, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 143.8, 137.1, 136.6, 132.3, 129.7, 129.0, 128.9, 127.1, 125.3, 123.4, 63.6, 21.6; Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.35; H, 5.61; N, 4.82.




**_N_-(2-(Hydroxymethyl)phenyl)benzamide (3.61c)**

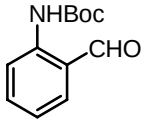
A solution of BzCl (1.0 mL, 8.9 mmol, 1.1 eq.) in $CHCl_3$ (9 mL) was dropwise added over 10 min. to an ice cold solution of 2-aminobenzyl alcohol (**3.60**) (1.0 g, 8.1 mmol, 1.0 eq.) and pyridine (0.78 mL, 9.7 mmol, 1.2 eq.) in $CHCl_3$ (40 mL). The obtained solution was stirred at room temperature for 20 h after which it was washed with aqueous 1 M HCl (2 portions of 50 mL), aqueous ½ saturated $NaHCO_3$ (50 mL), ½ brine (50 mL) and dried ($Na_2SO_4$). Removal of the solvent under vacuum afforded the title compound as a tanned solid (1.84 g, 91%) which was used without further purification.

[7.14] Consonni, R.; croce, P. D.; Ferraccioli, La Rosa, C. J. Chem. Soc., Perkin Trans. 1, 1996.

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.28; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.67 (s, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 7.88-7.93 (m, 2H), 7.50-7.57 (m, 1H), 7.42-7.49 (m, 2H), 7.34 (´t´d, *J* = 1.7, 7.6, 8.1 Hz, 1H), 7.16 (dd, *J* = 1.7, 7.6 Hz, 1H), 7.06 (´t´d, *J* = 1.1, 7.6, 7.6 Hz), 4.76 (s, 2H), 0.73 (brs, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 165.8, 138.1, 134.8, 132.1, 129.6, 129.4, 129.0, 128.9, 127.3, 124.4, 122.4, 65.0; LRMS (EI) *m/z* = 227 $[M]^+$.

**General procedure for the benzylic oxidation of *N*-protected 2-amino benzylic alcohols to the corresponding aldehydes with $MnO_2$ (GP 8):**

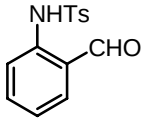
A suspension of the benzylic alcohol (1.0 eq.) and $MnO_2$ (4-5 eq.) (for the preparation of $MnO_2$ see Section 7.2) in $CH_2Cl_2$ (0.2 M in the benzylic alcohol) was refluxed under argon until TLC showed complete disappearance of starting material (typically 20-35 h), after which it was allowed to reach room temperature, diluted with $Et_2O$:$CH_2Cl_2$, 1:1 (v:v), stirred for 10 min. and filtrated through a pad of Celite. The filtrate was concentrated under vacuum, affording the crude aldehyde which was used without further purification.




***tert*-Butyl 2-formylphenylcarbamate**

Following GP 8, using *tert*-butyl 2-(hydroxymethyl)phenylcarbamate (**3.61a**) (2.0 g, 8.96 mmol). The title compound was obtained as a tan oil (1.22 g, 62%) which was used without further purification.

$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.43; mp 55-57 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.39 (brs, 1H), 9.89 (s, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 7.62 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.57 (ddd, *J* = 1.6, 7.4, 8.4 Hz, 1H), 7.13 (´t´d, *J* = 0.9, 7.4, 7.7 Hz), 1.53 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 195.3, 153.1, 142.0, 136.3, 136.2, 121.7, 121.4, 118.4, 81.2, 28.5; LRMS (EI) *m/z* = 221 $[M]^+$;; Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.21; H, 6.84; N, 6.20.

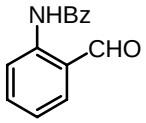



***N*-(2-Formylphenyl)-4-methylbenzenesulfonamide**

Following GP 8, using *N*-(2-(hydroxymethyl)phenyl)-4-methylbenzenesulfonamide (**3.61b**) (1.5 g, 5.4 mmol). The title compound was delivered as a beige solid (1.19 g, 80%) which was used without further purification.

$R_f$ (hexane:EtOAc, 1:1(v:v)) 0.56; mp 126-129 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ

10.79 (s, 1H), 9.83 (s, 1H), 7.75-7.78 (m, 2H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.59 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.51 (ddd, *J* = 1.5, 7.5, 8.3 Hz, 1H), 7.21-7.26 (m, 2H), 7.16 (´t´d, *J* = 0.9, 7.5, 7.6 Hz, 1H), 2.36 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ: 195.3, 144.4, 140.1, 136.5, 136.4, 136.1, 130.0, 127.5, 123.2, 122.0, 117.9, 21.8; LRMS (EI) *m/z* = 275 $[M]^+$; Anal. Calcd. for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09. Found: C, 60.92; H, 4.76; N, 4.95.



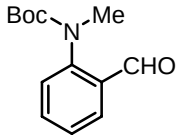

**_N_-(2-Formylphenyl)benzamide**

Following GP 8, using *N*-(2-(hydroxymethyl)phenyl)benzamide (**3.61c**) (1.29 g, 6.6 mmol). The title compound was delivered as a tan solid (1.18 g, 79%) which was used without further purification.

$R_f$ (1$^{st}$ elution: hexane:$Et_2O$, 3:1 (v:v); 2$^{nd}$ elution: hexane:$Et_2O$, 1:1 (v:v)) 0.45; mp 67-70 $^oC$; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 12.10 (brs, 1H), 10.00 (d, *J* = 0.4 Hz, 1H), 8.96 (d, *J* = 8.4 Hz, 1H), 8.06-8.09 (m, 2H), 7.73 (dd, *J* = 1.1, 7.6 Hz, 1H), 7.68 (dddd, *J* = 0.4, 1.5, 7.6, 7.9 Hz, 1H), 7.50-7.59 (m, 3H), 7.27 (´t´d, *J* = 1.1, 7.9, 8.4 Hz, 1); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 196.2, 166.4, 141.5, 136.6, 136.5, 134.5, 132.5, 129.1, 127.7, 123.3, 122.2, 120.2; LRMS (EI) *m/z* = 225 $[M]^+$; Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.55; H, 5.10; N, 6.07.

**General procedure for the *N*-methylation of *N*-protected 2-amino benzaldehydes (GP 9):**

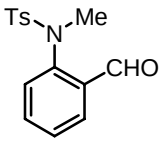
To a stirred ice cold suspension of NaH (1.15 eq.) in DMF (0.32 M) was dropwise added, over 15 min., a solution of the *N*-protected 2-aminobenzaldehyde (1.0 eq.) in DMF (0.4 M). After stirring at ice bath temperature for 10 min., the obtained solution was allowed to reach room temperature and stirred for further 15-20 min. after which it was re-cooled to 0 $^oC$ and a solution of MeI (1.3 eq.) in DMF (just enough to transfer the MeI quantitatively) was slowly added. Stirring continued at room temperature for 3 h, after which the solution was re-cooled to ice bath temperature and the reaction was quenched by slow addition of water. After partition between water and EtOAc:$Et_2O$ (1:1, (v:v)), the organic layer was further washed with water, dried ($Na_2SO_4$) and concentrated under vacuum to afford the *N*-methyl 2-aminobenzaldehydes which typically were used without further purification.




**_tert_-Butyl 2-formylphenyl(methyl)carbamate (3.62a)**

Following GP 8, using *tert*-butyl 2-formylphenylcarbamate (700 mg, 3.16 mmol). The title compound was obtained as a viscous oil (202 mg, 96 %), which was used without further purification.

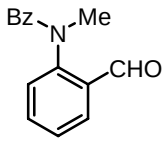
$R_f$ (1st elution: hexane:EtOAc, 1:1 (v:v); 2nd elution: hexane: $Et_2O$, 3:1 (v:v)) 0.70; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.09 (s, 1H), 7.88 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.60 (´t´d, *J* = 1.6, 7.7, 7.7 Hz, 1H), 7.37 (´t´, *J* = 7.7, 7.7 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 3.30 (s, 3H), 1.31 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 190.2, 155.7, 146.0, 136.2, 135.0, 132.4, 128.6, 127.3, 81.5, 38.2, 28.3; Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.31; H, 7.21; N, 6.14.




**_N_-(2-Formylphenyl)-_N_,4-dimethylbenzenesulfonamide (3.62b)**

Following GP 8, using *N*-(2-formylphenyl)-4-methylbenzenesulfonamide (700 mg, 2.54 mmol). The title compound was obtained a tan solid (723 mg, 98 %), which was used without further purification.

$R_f$ (1st elution: hexane:EtOAc, 1:1 (v:v); 2nd and 3rd elutions: hexane: $Et_2O$, 3:1 (v:v)) 0.53; mp 134-136 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ: 10.46 (s, 1H), 8.00-8.03 (m, 1H), 7.42-7.46 (m, 4H), 7.26-7.30 (m, 2H), 6.67-6.73 (m, 1H), 3.24 (s, 3H), 2.44 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ: 190.1, 144.5, 143.9, 135.1, 134.2, 132.8, 129.8, 128.6, 128.5, 128.4, 126.2, 39.1, 21.9; Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.25; H, 5.23; N, 4.68.




**_N_-(2-Formylphenyl)-_N_-methylbenzamide (3.62c)**

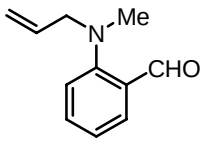
Following GP 8, using *N*-(2-formylphneyl)benzamide (700 mg, 3.1 mmol). The crude yellowish oil obtained was purified by flash chromatography on silica gel (hexane:EtOAc, 1:1 (v:v) with 1% $Et_3N$) affording the title compound as a yellow viscous oil (538 mg, 73%).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.22; mp 70-73 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.12 (s, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.53 (´t´, *J* = 7.0, 7.2 Hz, 1H), 7.35 (´t´, *J* = 7.0, 7.4 Hz, 1H), 7.07-7.26 (m, 6H), 3.52 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ: 190.0, 170.1, 144.8, 144.3, 142.9, 138.3, 137.7, 130.1, 129.2, 128.3, 125.0, 122.1, 39.4. LRMS (EI)

*m/z* = 239 $[M]^+$.

**General procedure for the preparation of the *ortho*-formyl-*N*-methylaniline derivatives (GP 10):**

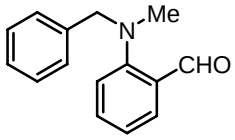
A suspension of 2-fluorobenzaldehyde (1.0 eq.), the *N*-methyamine derivative (2.0 eq.) and $K_2CO_3$ (2.0 eq.) in DMF (0.5 M with respect to 2-fluorobenzaldehyde) was heated to 105 °C to 110 °C for 30-40 h. The suspension obtained was allowed to reach room temperature, filtered and concentrated to 1/3 of its original volume, after which it was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic phases were washed with brine, dried ($Na_2SO_4$) and the solvent removed under vacuum. Purification by flash chromatography delivered the *ortho*-formyl-*N*-methylanilines.




**2-(Ally(methyl)amino)benzaldehyde (3.62d)**

Following GP 10, using *N*-methylallyamine (5.8 mL, 60.4 mmol, 3.0 eq.). Purification by flash chromatography (hexane:$Et_2O$, 3:1 (v:v)) delivered the title compound as a lemon oil (3.1 g, 89%).

$R_f$ (hexane:$Et_2O$, 3:1 (v:v)) 0.44; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.26 (d, 0.5 Hz, 1H), 7.78 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.46 (ddd, *J* = 1.8, 7.1, 8.3 Hz, 1H), 7.08 (dd, *J* = 0.4, 8.3 Hz, 1H), 7.03 (dd´t´, *J* = 0.4, 0.5, 7.1, 7.8 Hz, 1H), 5.91 (ddt, *J* = 5.9, 5.9, 10.2, 17.2 Hz, 1H), 5.28 (d´q´, *J* = 1.6,1.7, 1.7, 17.2 Hz, 1H; partial overlap with d´q´ at δ = 5.23 ppm), 5.23 (d´q´, *J* = 1.4, 1.4, 1.6, 10.2 Hz, 1H; partial overlap with d´q´ at δ = 5.28 ppm), 3.73, (d´t´, *J* = 1.4, 1.6, 5.9 Hz, 2H), 3.85 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 191.6, 155.7, 134.8, 134.3, 130.4, 127.9, 121.4, 119.1, 118.2, 62.3, 41.2; LRMS (EI) *m/z* = 175 $[M]^+$; Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.26; H, 7.37; N, 8.00.

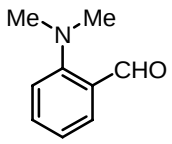



**2-(Benzyl(methyl)amino)benzaldehyde (3.62e)**

Following GP 10, using *N*-methylbenzylamine (5.2 mL, 40.2 mmol, 2.0 eq.). Purification by flash chromatography (hexane: $Et_2O$, 3:1 (v:v)) delivered the title compound as a lemon yellow oil (4.2 g, 92%).

$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.38; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.40 (d, *J* = 0.5 Hz, 1H), 7.83 (dd, *J* = 1.7, 7.7 Hz, 1H), 7.48 (ddd, *J* = 1.7, 7.1, 8.3 Hz, 1H), 7.27-7.36 (m, 5H), 7.10 (dd, *J* = 0.6, 8.3 Hz, 1H, partial overlap with ´t´t at δ = 7.07 ppm), 7.07 (´t´t,

*J* = 0.6, 0.6, 7.1, 7.7 Hz, 1H, partial overlap with dd at δ = 7.10 ppm), 4.34 (s, 2H), 2.82 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 191.6, 155.9, 137.6, 134.9, 130.4, 128.8, 128.7, 128.2, 127.7, 121.9, 119.7, 62.6, 42.5; LRMS (EI) *m/z* = 225 $[M]^+$; Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.23; H, 6.50; N, 6.33.




**2-(Dimethylamino)benzaldehyde (3.62f)**

The following modification of GP 10 was used:[7.15] a suspension of 2-fluorobenzaldehyde (1.0 g, 8.0 mmol, 1.0 eq.), dimethylamine hydrochloric salt (855 mg, 10.5 mmol, 1.3 eq.) and $K_2CO_3$ (1.11 g, 8.0 mmol, 1.0 eq.) in DMF (17 mL) and water (7 mL) was heated to gentle reflux (105-110 °C). After approximately 4 h a second portion of dimethylamine hydrochloric salt (400 mg, 4.9 mmol, 0.6 eq.) and $K_2CO_3$ (1.11 g, 8.0 mmol, 1.0 eq.) were added and heating continued for further 4 h. The suspension obtained was allowed to reach room temperature, filtered and the filtrate partitioned between $Et_2O$ (100 mL) and aqueous saturated $NaHCO_3$ (40 mL). The aqueous layer was further extracted with $Et_2O$ (2 portions of 30 mL) and the combined organic layers were washed with water (30 mL), brine (15 mL), dried ($Na_2SO_4$) and solvent removed in vacuum. The residue obtained was purified by flash chromatography (hexane: $Et_2O$, 3:1 (v:v)) to afford the title compound as a bright yellow oil (1.1 g, 92%).

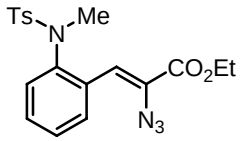
$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.30; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 10.21 (s, 1H), 7.75 (dd, *J* = 1.7, 7.7 Hz, 1H), 7.45 (ddd, *J* = 1.7, 7.2, 8.9 Hz, 1H), 7.03 (´d´, *J* = 8.9 Hz, 1H), 6.98 (´t´, *J* = 7.2, 7.7 Hz, 1H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 191.4, 156.0, 134.8, 131.2, 127.2, 120.8, 117.8, 45.8; EI-MS *m/z*: 149 $[M^+]$; Anal. Calcd. for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.23; H, 7.22; N, 9.16.

**General procedure for the preparation of the azido carboxylates (Hemetsberger substrates) (GP 11):**

Sodium metal (9 eq.) is dissolved in EtOH (1.5 M). To the resulting solution was slowly added, at -15 °C, over 1 h, a solution of protected *N*-methyl 2-aminobenzaldehyde (1.0 eq.) and ethyl azido acetate (commercially available as a 2.39 M solution in EtOH, 10 eq.), during which period a turbid suspension formed. After stirring at -15 °C to -10 °C for 5-7 h, the temperature was allowed to slowly reach 0 °C to room temperature and stirring continued for further 3-5 h. The

[7.15] Rodríguez, J. G.; Lafuente, A.; Martín-Vilamil, R.; Martínez-Alcazar, M. P. *J. Phys. Org. Chem.* **2001**, *14*, 859.

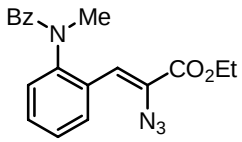
suspension obtained was then re-cooled to 0 °C and quenched with aqueous saturated $NH_4Cl$ and gently partitioned between $Et_2O$:EtOAc, 1:1 (v:v) and aqueous ½ saturated $NH_4Cl$. The aqueous layer was further extracted with $Et_2O$:EtOAc, 1:1 (v:v) and the combined organic layers were washed with aqueous ½ saturated brine and dried ($Na_2SO_4$). The obtained solution was then concentrated to 15-20 mL and filtered through a short column of silica gel ($Et_2O$). Removal of the solvent under vacuum and purification by flash chromatography on silica gel delivered the azido carboxylates.




**(*Z*)-Ethyl 2-azido-3-(2-(*N*,4-dimethylphenylsulfonamido) phenyl)acrylate (3.63b)**

Following GP 11, using *N*-(2-formylphenyl)-*N*,4-dimethylbenzenesulfonamide (**3.62b**) (185 mg, 0.63 mmol). Purification by flash chromatography on silica gel (hexane:EtOAc, 1:1 (v:v)) afforded the title compound as a pale yellow solid (121 mg, 48%).

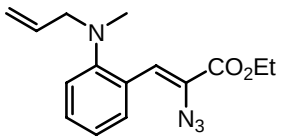
$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.58; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 8.24 (dd, *J* = 1.4, 7.9 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.53 (´t´dd, *J* = 0.8, 1.2, 7.6, 7.9 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.26 (s, 1H), 7.22 (´t´d, *J* = 1.4, 7.6, 7.9 Hz, 1H), 6.81 (dd, *J* = 1.2, 7.9 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.14 (s, 3H), 2.44 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 163.6, 144.0, 140.9, 134.7, 133.5, 131.1, 129.9, 129.7, 128.4, 127.8, 127.0, 120.8, 62.6, 39.5, 21.8, 14.4.




**(*Z*)-Ethyl 2-azido-3-(2-(*N*-methyl benzamido)phenyl) acrylate (3.63c)**

Following GP 11, using *N*-(2-formylphenyl)-*N*-methylbenzamide (**3.62c**) (300 mg, 1.25 mmol). Purification by flash chromatography in silica gel (hexane:EtOAc, 1:1 (v:v)) afforded the title compound as a viscous yellow oil (215 mg, 49%).

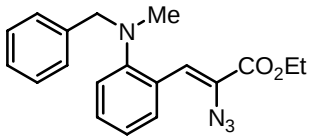
$R_f$ (1$^{st}$ elution: hexane:$Et_2O$, 3:1 (v:v); 2$^{nd}$ elution: hexane: $Et_2O$, 1:1 (v:v)) 0.34; $^1$H-NMR (d-acetone, 300 MHz) δ 8.03 (d, *J* = 6.6 Hz, 1H), 7.12-7.38 (m, 8H), 6.96 (s,1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); $^{13}$C-NMR (d-acetone, 75 MHz) δ 170.2, 163.0, 144.5, 136.5, 130.7, 130.6, 130.4, 129.7, 129.0, 128.5, 128.1, 127.7, 127.5, 119.4, 62.5, 37.8, 13.8.



**(*Z*)-Ethyl 3-(2-allyl(methyl)amino)phenyl)-2-azido acrylate (3.63d)**

Following GP 11, using 2-(ally(methyl)amino) benzaldehyde (**3.62d**) (300 mg, 1.7 mmol). Purification by flash chromatography in silica gel (hexane: $Et_2O$, 3:1 (v:v)) delivered the title compound as a yellow solid (337 mg, 69%).

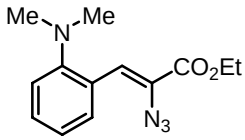
$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.55; mp 38-40 $^oC$; $^1H$-NMR ($CDCl_3$, 300 MHz) δ 8.03 (ddd, $J$ = 0.4, 1.8, 8.4 Hz, 1H), 7.32 (s, 1H; partial overlap with ddd at δ = 7.29 ppm), 7.29 (ddd, $J$ = 1.8, 7.3, 8.2 Hz, 1H; partial overlap with s at δ = 7.32 ppm), 7.01-7.06 (m, 2H), 5.92 (ddt, $J$ = 6.0, 6.0, 10.2, 17.1 Hz, 1H), 5.28 (d´q´, $J$ = 1.6,1.6, 1.6, 17.2 Hz, 1H), 5.20 (d´q´, $J$ = 1.2, 1.2, 1.2, 10.2 Hz, 1H), 4.37 (q, $J$ = 7.1 Hz), 3.46 (´d´, $J$ = 6.0 Hz, 2H), 2.72 (s, 3H), 1.41 (t, $J$ = 7.1 Hz, 3H); $^{13}C$-NMR ($CDCl_3$, 75 MHz) δ 164.2, 153.1, 135.3, 130.8, 130.1, 126.7, 124.9, 123.6, 121.9, 118.9, 117.7, 62.3, 61.8, 40.0, 14.5; LRMS (MS) *m/z* = 286 $[M]^+$; Anal. Calcd. for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57. Found: C, 63.13; H, 6.23; N, 19.33.



**(Z)-Ethyl 2-azido-3-(2-(benzyl(methyl)amino)phenyl) acrylate (3.63e)**

Following GP 11, using 2-(benzyl(methyl)amino)benzaldehyde (**3.62e**) (385 mg, 1.7 mmol). Purification by flash chromatography on silica gel (hexane: $Et_2O$, 3:1 (v:v)) delivered the title compound as a tanned oil (417 mg, 72%).

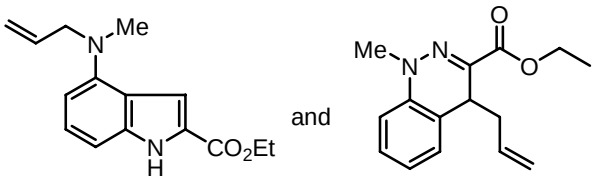
$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.54; $^1H$-NMR ($CDCl_3$, 300 MHz) δ 8.07 (ddd, $J$ = 0.4, 1.9, 8.2 Hz, 1H), 7.53 (s, 1H), 7.27-7.39 (m, 6H), 7.07-7.12 (m, 2H), 4.31 (q, $J$ = 7.1 Hz, 2H), 4.05 (s, 2H), 2.64 (s, 3H), 1.37 (t, $J$ = 7.1 Hz, 3H); $^{13}C$-NMR ($CDCl_3$, 75 MHz) δ 164.1, 153.1, 138.5, 130.9, 130.3, 128.6, 128.5, 127.4, 127.2, 125.3, 123.3, 122.5, 119.6, 62.6, 62.3, 40.8, 14.5; LRMS (EI) *m/z* = 336 $[M]^+$;



**(Z)-Ethyl 2-azido-3-(2-dimethylamino)phenylacrylate (3.63f)**

Following GP 11, using 2-(dimethylamino)benzaldehyde (**3.62f**) (400 mg, 2.7 mmol). Purification by flash chromatography on silica gel (hexane: $Et_2O$, 3:1 (v:v)) delivered the title compound as a tanned oil (456 mg, 65%).

$R_f$ (hexane: $Et_2O$, 3:1 (v/v)) 0.46; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 8.01 (dd, *J* = 1.6, 8.3 Hz, 1H), 7.25-7.32 (m, 2H), 7.00-7.06 (m, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 2.74 (s, 6H), 1.40 (t, *J* = 7.2 Hz, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 164.2, 153.7, 130.8, 130.2, 126.5, 124.9, 123.9, 121.8, 118.0, 62.3, 45.2, 14.5; LRMS (EI) *m/z* = 232 $[M-N_2]^+$.

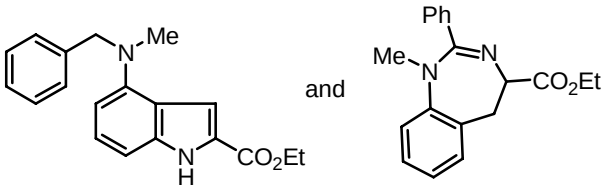



**Ethyl 4-(allyl(methyl)amino)-1*H*-indole-2-carboxylate (3.64d)**
and
**Ethyl 4-allyl-1-methyl-1,4-dihydrocinnoline-3-carboxylate (3.65)**

A solution of (*Z*)-ethyl 3-(2-allyl(methyl)amino)phenyl)-2-azidoacrylate (**3.63d**) (98 mg, 0.34 mmol) in toluene (2.2 mL) was inserted in an oil bath previously heated to 115 °C and refluxed for 6½ h, after which the solvent was removed under vacuum. The tanned oil obtained was then purified by (repeated) PTLC (hexane:$Et_2O$, 1:1 (v:v), double elution) affording the desired ethyl 4-(allyl(methyl)amino)-1*H*-indole-2-carboxylate (**3.64d**) as a pale yellow solid (13 mg, 15%), ethyl 4-allyl-1-methyl-1,4-dihydrocinnoline-3-carboxylate (**3.65**) as a yellow oil (18 mg, 20%) and other unidentified by-products.

For Ethyl 4-(allyl(methyl)amino)-1*H*-indole-2-carboxylate (**3.64d**): $R_f$ (hexane:$Et_2O$, 3:1 (v:v); double elution) 0.42; $^1$H-NMR (*d*-acetone, 300 MHz) δ 10.87 (brs, 1H), 7.24 (s, 1H), 7.14 (′t′, *J* = 7.8, 8.1 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.45 (d, *J* = 7.8 Hz, 1H), 6.04 (ddt, *J* = 5.3, 5.3, 10.4, 17.2 Hz, 1H), 5.37 (d′q′, *J* = 1.8, 1.8, 1.9, 17.2 Hz, 1H), 5.24 (d′q′, *J* = 1.6, 1.6, 1.9, 10.4 Hz, 1H), 4.34 (q, 7.1 Hz, 2H), 3.98 (d′t′, *J* = 1.6, 1.8, 5.3 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); $^{13}$C-NMR (*d*-acetone, 75 MHz) δ 161.5, 147.2, 139.5, 135.6, 126.0, 125.9, 119.9, 116.1, 107.7, 105.4, 104.5, 60.4, 58.1, 38.7, 14.1.

For ethyl 4-allyl-1-methyl-1,4-dihydrocinnoline-3-carboxylate (**3.65**): $R_f$ (hexane:$Et_2O$, 3:1 (v:v); double elution) 0.39; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.28 (′t′d, *J* = 8.2, 7.6, 1.4 Hz, 1H), 7.19 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.11 (′t′, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 5.65 (ddt, *J* = 7.3, 7.3, 10.1, 17.3 Hz, 1H), 4.89 (d, 10.1 Hz, 1H), 4.81 (d, *J* = 17.0 Hz, 1H), 3.70 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 1H, partial overlap to t at δ = 4.19 ppm), 4.19 (t, *J* = 6.4 Hz, 1H, partial overlap to q at δ = 4.25 ppm), 3.56 (s, 3H), 2.17 (′t′, *J* = 6.9 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).

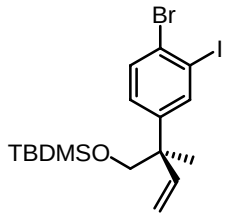



**Ethyl 4-(benzyl(methyl)amino)-1*H*-indole-carboxylate (3.64e)**
and
**(*Z*)-Ethyl 1-methyl-2-phenyl-4,5-dihydro-*1H*-benzo[d][1,3]diazepine-4-carboxylate (3.66)**

A solution of (*Z*)-ethyl 2-azido-3-(2-(benzyl(methyl)amino)phenyl) acrylate **(3.63e)** (120 mg, 0.35 mmol) in toluene (2.2 mL) was inserted in an oil bath previously heated to 115 $^{o}$C and refluxed for 6½ h, after which the solvent was removed under vacuum. The tanned oil obtained was then purified by (repeated) PTLC (hexane:$Et_2O$, 1:1 (v:v), double elution) affording the desired ethyl 4-(benzyl(methyl)amino)-1*H*-indole-carboxylate (**3.64e**) (17 mg, 15%), (*Z*)-Ethyl 1-methyl-2-phenyl-4,5-dihydro-*1H*-benzo[d][1,3]diazepine-4-carboxylate (**3.66**) (21 mg, 20%), and other unidentified by-products.

For ethyl 4-(benzyl(methyl)amino)-1*H*-indole-carboxylate (**3.64e**): $R_f$ (hexane:$Et_2O$, 1:1 (v:v); double elution) 0.56; $^{1}$H-NMR (*d*-acetone, 300 MHz) δ 10.90 (brs, 1H), 7.30-7.45 (m. 6H), 7.16 (dd, *J* = 7.6, 8.2 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.40 (dd, *J* = 0.7, 7.6 Hz, 1H), 4.60 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.18 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); $^{13}$C-NMR (*d*-acetone, 75 MHz) δ 161.5, 147.2, 139.6, 139.4, 128.6, 127.7, 127.1, 126.1, 120.0, 107.5, 105.8, 104.8, 104.7, 60.4, 59.2, 39.2, 14.0.

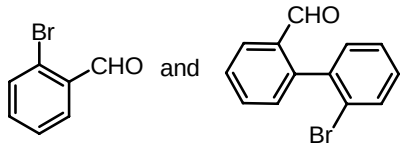
For (*Z*)-Ethyl 1-methyl-2-phenyl-4,5-dihydro-*1H*-benzo[d][1,3]diazepine-4-carboxylate (**3.66**): $R_f$ (hexane:$Et_2O$, 1:1 (v:v); double elution) 0.49; $^{1}$H-NMR ($CDCl_3$, 300 MHz) δ 6.81-7.30 (m, 9H), 4.34 (dd, *J* = 5.7, 7.5 Hz, 1H), 4.18 (q, *J* = 6.9 Hz, 1H), 4.17 (q, *J* = 6.9 Hz, 1H), 3.47 (s, 3H), 2.73 (dd, *J* = 5.7, 12.8 Hz, 1H), 2.62 (dd, *J* = 7.5, 12.8 Hz, 1H), 1.27 (t, *J* = 6.9 Hz); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 163.9, 138.8, 138.1, 132.7, 129.8, 128.6, 128.0, 127.7, 126.4, 123.8, 121.6, 111.4, 60.5, 40.9, 38.1, 14.0.




**(*R*)-(2-(4-Bromo-3-iodophenyl)-2-methylbut-3-enyloxy)(*tert*-butyl)dimethylsilane (3.73)**

To a solution of TBDMSCl (131 mg, 0.89 mmol, 1.3 eq.) and imidazole (122 mg, 1.77 mmol, 2.6 eq.) in DMF (0.65 mL) was added a solution of (crude) (*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-en-1-ol (**3.46**) (245 mg, 0.66 mmol, 1.0 eq.) in DMF (1.35 mL) at room temperature. After stirring at this temperature over 7 h, the resulting solution was partitioned between aqueous 1 M HCl (15 mL) and $Et_2O$ (25 mL). The organic layer was washed with a second portion of aqueous 1 M HCl (15 mL) and the combined acidic layers were extracted with $Et_2O$ (10 mL). The combined organic layers were washed with aqueous ½ saturated $NaHCO_3$ (25 mL), brine (15 mL), dried ($Na_2SO_4$) and concentrated under vacuum to afford a pale yellow residue. Purification by flash chromatography on silica gel (hexane: $Et_2O$, 3:1 (v:v)) delivered the title compound as a clear oil (254 mg, 80%).

$R_f$ (hexane: $Et_2O$ 3:1 (v:v)) 0.69; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.89 (d, $J$ = 2.2 Hz, 1H), 7.55 (d, $J$ = 8.4 Hz, 1H), 7.23 (dd, $J$ = 2.2, 8.4 Hz, 1H), 6.04 (dd, $J$ = 10.9, 17.6 Hz, 1H), 5.21 (dd, $J$ = 1.2, 10.9 Hz, 1H), 5.10 (dd, $J$ = 1.2, 17.6 Hz, 1H), 3.70 (s, 2H), 1.37 (s, 3H), 0.88 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 152.3, 148.8, 145.1, 137.5, 134.5, 132.5, 119.7, 106.3, 75.7, 51.9, 31.4, 28.2, 23.8, 0.0; LRMS (EI) *m/z* = 482 $[M]^+$; $[\alpha]_D^{25}$ -10.9 (*c* 2.3, $CHCl_3$).




**2-Bromobenzaldehyde**
and
**2-Bromo-2'-formylbiphenyl (3.75)**

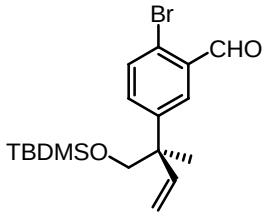
**Procedure I**: To a slurry of *ortho*-iodobromobenzene (200 mg, 0.71 mmol, 1.0 eq.) and DMF (115 µL, 1.56 mmol, 2.2 eq.) in toluene (7 mL) at -105 °C to 100 °C was added in a dropwise manner over 3-4 min. a solution of $^n$BuLi in hexanes (1.6 M, 0.55 mL, 0.88 mmol, 1.25 eq.). After stirring at -105 °C to -100 °C for 2 h, the temperature was allowed to increase to -30 °C over 1 h, after which period the cooling bath was replaced by a water bath and the pale yellow solution was stirred at room temperature for 20 min.. The resulting solution was partitioned between water (20 mL) and $Et_2O$ (45 mL); the aqueous layer was further extracted with $Et_2O$ (10 mL) and the combined organic layers were washed with aqueous ½ saturated brine (20 mL), dried ($MgSO_4$) and concentrated under vacuum to afford a yellow oil. Purification by PTLC (1$^{st}$ elution: hexane:$CH_2Cl_2$, 2.5:1, (v:v); 2$^{nd}$ elution: hexane:ether, 3:1 (v:v)) delivered

2-bromobenzaldeyhde as yellow oil (78 mg, 60%).

**Procedure II**: To a slurry of *ortho*-iodobromobenzene (200 mg, 0.71 mmol, 1.0 eq.) in a mixture of $Et_2O$:THF, 1:1 (v:v) (23 mL) at -115 °C to -110 °C was added in a dropwise manner over 3-4 min. a solution of $^n$BuLi in hexanes (1.6 M, 0.47 mL, 0.74 mmol, 1.05 eq.). After stirring at this temperature for approximately 2 min., DMF (250 µL, 3.2 mmol, 4.5 eq.) was added dropwise over 8-10 min. and stirring continued at -110 °C for 3 h further. The temperature was gradually increased to -35 °C over 20 min., at which time the cooling bath was removed and stirring continued for further 15 min. The resulting solution was subjected to similar work-up and purification procedures as described in procedure I above affording 2-bromobenzaldeyhde as a pale yellow oil (20 mg, 15%) and 2-bromo-2'formylbiphenyl (**3.75**) (9 mg, 5%).

For 2-bromobenzaldehyde: $R_f$ (hexane:$CH_2Cl_2$, 2.5:1 (v:v)) 0.25; $^1$H-NMR (d-acetone, 300 MHz) δ 10.33 (d, $J$ = 0.7 Hz, 1H), 7.88-7.91 (m, 1H), 7.77-7.80 (m, 1H), 7.55-7.65 (m, 2H).

For 2-bromo-2'-formylbiphenyl (**3.75**): $R_f$ (hexane:$CH_2Cl_2$, 2.5:1 (v:v)) 0.2; $^1$H-NMR (d-acetone, 300 MHz)[7.16] δ 9.78 (s, 1H), 8.00 (dd, $J$ = 1.5, 7.7 Hz), 7.75-7.82 (m, 2H), 7.62-7.68 (m, 1H), 7.52-7.58 (m, 1H), 7.37-7.48 (m, 3H).



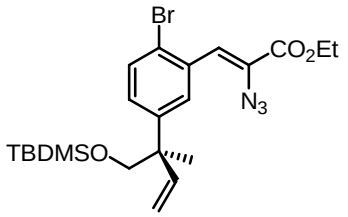

**(*R*)-2-Bromo-5-(2-((*tert*-butyldimethylsilyloxy)methyl) but-3-en-2-yl)benzaldehyde (3.74)**

To a -105 °C to -100 °C cold slurry of (*R*)-(2-(4-bromo-3-iodophenyl)-2-methylbut-3-enyloxy) (*tert*-butyl) dimethylsilane (**3.73**) (429 mg, 0.89 mmol, 1.0 eq.) in toluene (14.8 mL) was added a solution of $^n$BuLi in hexanes (1.6 M, 1.02 mmol, 0.64 mL, 1.15 eq.) over 8 sec.. After stirring at this temperature for 2 min., DMF (193 µL, 2.49 mmol, 2.8 eq.) was added over 5 sec.. The resulting pale yellow solution was stirred at -103 °C to -95 °C for 1½ h and then allowed to reach -40 °C over ½ h, after which the cooling bath was replaced by a water bath and stirring continued for further 10 min.. The resulting pale yellow solution was then partitioned between $Et_2O$ (80 mL) and water (15 mL) and the aqueous layer was extracted with $Et_2O$ (2 portions of 20 mL). The combined organic layers were washed with ½ brine (20 mL), dried

[7.16] Oba, M.; Iida, M.; Nishiyama, K. *Organometallics* **2001**, *20*, 4287.

($Na_2SO_4$) and concentrated under vacuum affording a pale yellow oil. Purification by flash chromatography on silica gel (hexane→hexane: $Et_2O$, 6:1 (v:v)) delivered the title compound as a colorless oil (242 mg, 71%).

$R_f$ (1st elution: hexane: $Et_2O$, 6:1 (v:v); 2nd elution: hexane) 0.71; $^1$H-NMR (*d*-acetone, 300 MHz) δ 10.34 (s, 1H), 7.95 (d, *J* = 2.5 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.65 (dd, *J* = 2.5, 8.4 Hz 1H), 6.16 (dd, *J* = 10.9, 17.6 Hz, 1H), 5.23 (dd, *J* = 1.2, 10.9 Hz, 1H), 5.17 (dd, *J* = 1.2, 17.6 Hz, 1H), 3.86 (d, *J* = 0.8 Hz, 2H), 1.45 (s, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 191.3, 146.5, 143.6, 135.3, 133.6, 133.1, 129.0, 124.0, 113.9, 70.2, 46.8, 25.5, 22.2, 18.0, -6.2; LRMS (EI) *m/z* = 384 $[M]^+$.

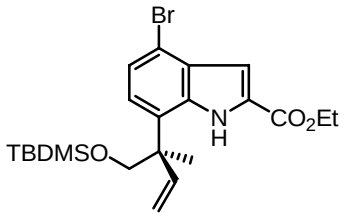



**(*R,Z*)-Ethyl 2-azido-3-(2-bromo-5-(2-((*tert*-butyl dimethylsilyloxy)methyl)but-3-en-2-yl)phenyl) acrylate (3.77)**

Sodium metal (35.9 mg, 1.56 mmol, 6.0 eq.) was dissolved in EtOH (1.0 mL). To the resulting solution was slowly added, at -15 °C and over 1 h, a solution of (*R*)-2-Bromo-5-(2-((*tert*-butyldimethylsilyloxy)methyl)but-3-en-2-yl)benzaldehyde (**3.74**) (100 mg, 0.26 mmol, 1.0 eq.) and ethyl azido acetate (0.71 mL of a 2.39 M solution in EtOH, 1.69 mmol, 6.5 eq.). During addition a milky pale yellowish suspension formed. The temperature was then allowed to rise to -15 °C to -10 °C and stirring continued for 18 h further. The orange suspension obtained was then stirred at room temperature for ½ h, re-cooled to ice bath temperature, quenched with aqueous saturated $NH_4Cl$ (0.7 mL) and gently partitioned between $Et_2O$:EtOAc (1:1 (v:v)) (30 mL) and aqueous ½ saturated $NH_4Cl$ (10 mL). The deep tan aqueous layer was further extracted with $Et_2O$ :EtOAc (1:1 (v:v)) (3 portions of 10 mL); the combined organic layers were washed with aqueous ½ saturated brine (10 mL) and dried ($Na_2SO_4$). The obtained tan solution was then concentrated to 5 mL and filtered through a short column of silica gel ($Et_2O$). After removal of the solvent under vacuum, a reddish oil was obtained which was purified by PTLC (hexane:$Et_2O$, 3:1 (v:v)). The title compound was obtained as a colorless oil (78 mg, 60%).

$R_f$ (1st elution: hexane: $Et_2O$, 3:1 (v:v); 2nd elution: pentane) 0.63 (note: the Rf values the starting material and the product are very similar); $^1$H-NMR ($CDCl_3$, 300 MHz) δ 8.14 (d, *J* = 2.4 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 2.6 Hz, 1H), 7.23 (dd, *J* = 2.6, 8.5 Hz, 1H), 6.11 (dd, *J* = 10.9, 17.6 Hz, 1H), 5.23 (dd, *J* = 1.2, 10.9 Hz, 1H),

5.13 (dd, *J* = 1.2, 17.6 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 3.77 (d, *J* = 1.6 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H; partial overlap with s at δ = 1.43 ppm), 1.43 (s, 3H; partial overlap with s at δ = 1.46 ppm), 0.88 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 169.0, 150.6, 149.3, 137.8, 137.7, 136.0, 135.4, 132.7, 129.6, 128.3, 119.5, 76.0, 68.1, 52.3, 31.4, 28.2, 23.9, 19.9, 0.0.

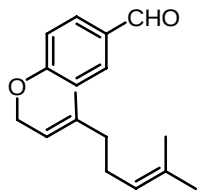



**(*R*)-Ethyl-4-bromo-7-(1-tert-butyldimethylsilyoxy)-2-methylbut-3-en-2-yl)-1*H*-indole-2-carboxylate (3.78)**

A solution of (*R*,*Z*)-ethyl 2-azido-3-(2-bromo-5-(1-*tert*-butyldimethylsilyoxy)-2-methylbut-3-en-2-yl)phenyl) acrylate (**3.77**) (74 mg, 0.14 mmol) in *meta*-xylene (1.3 mL) was dropwise added over 1 h to refluxing *meta*-xylene (3.7 mL). The obtained solution was refluxed for 3½ h further, after which the solvent was removed under vacuum to afford a tanned oil. Purification by PTLC (hexane:$Et_2O$, 5:1 (v:v)) afforded the title compound as a pale yellow oil (45 mg, 69%).

$R_f$ (hexane: $Et_2O$, 5:1) 0.27; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.87, (brs, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 6.24 (dd, *J* = 10.8, 17.7 Hz, 1H), 5.40 (dd, *J* = 1.1, 10.8 Hz, 1H), 5.31 (dd, *J* = 1.1, 17.7 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.02 (d, *J* = 10.0 Hz, 1H), 3.87 (d, *J* = 10.0 Hz, 1H), 1.51 (s, 3H), 1.46 (t, *J* = 7.1 Hz), 0.87 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 167.3, 149.3, 141.7, 134.5, 134.0, 133.0, 129.8, 129.0, 120.5, 120.4, 113.9, 76.2, 66.8, 52.3, 31.6, 28,8, 24.1, 20.1, 0.0; LRMS (EI) *m/z* = 465 $[M]^+$; $[\alpha]_D^{25}$ +22.7 (*c* 2.15 in $CHCl_3$).

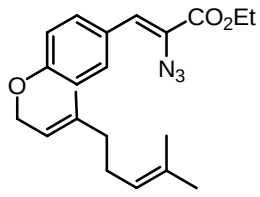
## 7.4 – Experimental Procedure for Chapter 5 (Teleocidins B)




**(*E*)-4-(3,7-dimethylocta-2,6-dienyloxy)benzaldehyde (5.1)**

Following a literature procedure,[7.17] a suspension of *para*-hydroxybenzaldehyde (1.0 g, 8.2 mmol, 1.0 eq.), geranyl bromide (2.3 g, 10.6 mmol, 1.3 eq.) and $K_2CO_3$ (2.0 g, 14.7 mmol, 1.8 eq.) in acetone (54 mL) was refluxed for 4 h. The resulting suspension was cooled to ice bath temperature, quenched with $H_2O$ (10 mL), concentrated to 1/3 of its initial volume and partitioned between water (50 mL) and $Et_2O$ (60 mL). The aqueous layer was further extracted with EtOAc (2 portions of 60 mL). The combined organic layers were washed with ½ brine (50 mL), dried ($MgSO_4$) and concentrated under vacuum. Purification by flash chromatography (hexane:$Et_2O$, 3:1 (v:v) with 1% $NEt_3$) afforded the title compound as a light yellow oil (2.10 g, quantitative).

$R_f$ (hexane: $Et_2O$, 1:1 (v:v)) 0.50;$^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.87 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.0 (d, *J* = 8.8 Hz, 2H), 5.47 (tq, *J* = 6.5, 1.2 Hz, 1H), 5.05-5.12 (m, 1H), 4.62 (d, *J* = 6.5 Hz, 2H), 2.06-2.16 (m, 4H), 1.74 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 191.1, 164.2, 142.4, 132.2, 130.0, 123.9, 118.8, 115.2, 65.5, 39.7, 34.5, 26.4, 25.9, 18.0, 17.0.

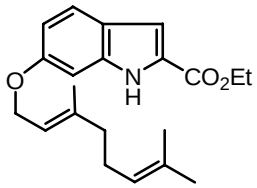



**(*Z*)-Ehtyl 2-azido-3-(4-((*E*)-3,7-dimethylocta-2,6-dienyloxy)phenyl)acrylate (5.2)**

Following GP 11, using (*E*)-4-(3,7-dimethylocta-2,6-dienyloxy)benzaldehyde (**5.1**) (2.10 g, 8.1 mmol). Purification by flash chromatography on silica gel (hexane: $Et_2O$, 3:1 (v:v)) delivered the title compound as a viscous yellow oil (2.3 g, 76%).

$R_f$ (hexane: $Et_2O$, 1:1 (v:v)) 0.58;$^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.48 (tq, *J* = 6.5, 1.2 Hz, 1H), 5.05-5.12 (m, 1H), 4.57 (d, *J* = 6.5 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.06-2.16 (m, 4H), 1.75 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.39 (t. *J* = 7.1 Hz, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 164.1, 160.0, 141.9, 132.6, 132.1, 126.1, 125.7, 124.0, 123.4, 119.3, 114.8, 65.2, 62.3, 39.8, 26.5, 25.9, 18.0, 16.9, 14.5.

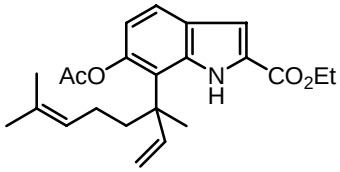
[7.17] Shinmon, N.; Cava, M. *J. Chem. Soc., Chem. Commun.* **1980**, 1020.



**Ethyl 6-((*E*)-3,7-dimethylocta-2,6-dineyloxy)-1*H*-indole-2-carboxylate (5.3)**

A solution of (*Z*)-ehtyl 2-azido-3-(4-((*E*)-3,7-dimethylocta-2,6-dienyloxy)phenyl)acrylate (**5.2**) (550 mg, 1.48 mmol) in toluene (17 mL) was inserted in an oil bath previously heated to 115 $^{o}$C. The obtained solution was refluxed for 3 h, after which the solvent was removed under vacuum to afford the title compound as a pale yellow solid (506 mg, quantitative), which was used without further purification.

$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.23; mp 111-113 $^{o}$C; $^{1}$H-NMR ($CDCl_3$, 300 MHz) δ 8.80 (brs, 1H), 7.53 (d, *J* = 9.5 Hz, 1H), 7.16 (d, *J* = 1.56 Hz, 1H), 6.82-6.86 (m, 2H), 5.53 (td, *J* = 6.5, 1.0 Hz, 1H), 5.06-5.14 (m, 1H), 4.57 (d, *J* = 6.5 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.05-2.17 (m, 4H), 1.76 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 162.2, 158.3, 141.6, 138.1, 132.1, 126.6, 124.0, 123.6, 122.0, 119.6, 113.0, 109.2, 94.9, 65.4, 61.0, 39.8, 26.5, 25.9, 18.0, 17.0, 14.7.

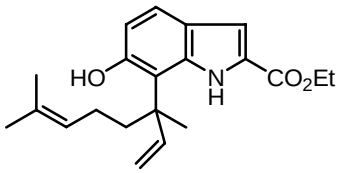


**Ethyl 6-acetoxy-7-(3,7-dimethylocta-1,6-dien-3-yl)-1*H*-indole-2-carboxylate (5.7c)**

A solution of ethyl 6-((*E*)-3,7-dimethylocta-2,6-dineyloxy)-1*H*-indole-2-carboxylate (**5.3**) (100 mg, 0.29 mmol) in dimethylaniline (2.0 mL) and $Ac_2O$ (2.0 mL) in a closed, thick wall glass container was inserted in a salt bath (53% $KNO_3$, 40% $NaNO_2$ and 7% $NaNO_3$, by weight) at 195 $^{o}$C until TLC showed no more starting material (approximately 6-7 h). After reaching room temperature, the reaction mixture was poured into iced-water (approximately 100 mL), stirred vigorously for 10 min and extracted with $Et_2O$ (2 portions of 50 mL). The combined organic layers were washed with aqueous 5% HCl (2 portions of 30 mL), aqueous saturated $NaHCO_3$ (2 portions of 30 mL), brine (15 mL) and dried ($MgSO_4$). After removal of the solvent under vacuum, the obtained tan residue was purified by flash chromatography (hexane:$Et_2O$, 2:1 (v:v)) affording the title compound as a pale yellow oil (71 mg, 61%).

$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.25 (note: the Rf values the starting material and the product are very similar; ;$^{1}$H-NMR ($CDCl_3$, 300 MHz) δ 9.6 (brs, 1H), 7.53 (dd, *J* = 0.6, 8.6 Hz, 1H), 7.13 (d, *J* = 2.2 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 6.50 (dd, *J* = 10.8, 17.8 Hz, 1H), 5.38 (dd, J = 0.8, 17.8 Hz, 1H), 5.36 (dd, *J* = 0.8, 10.8 Hz, 1H), 5.00-

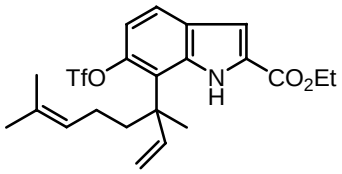
5.07 (m, 1H) 4.37 (q, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 1.96 (s, 3H), 1.63 (s, 3H), 1.59 (s, 3H), 1.45 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 170.4, 162.0, 148.8, 146.8, 132.1, 127.6, 127.0, 124.4, 121.9, 118.7, 112.2, 108.2, 61.2, 45.6, 40.2, 26.1, 25.9, 23.9, 21.9, 17.8, 14.6.




**Ethyl 6-hydroxy-7-linalyl-1*H*-indole-2-carboxylate (5.7a)**

A solution of ethyl 6-((*E*)-3,7-dimethylocta-2,6-dineyloxy)-1*H*-indole-2-carboxylate (**5.3**) (1.42 g, 4.16 mmol, 1.0 eq.), HMDS (8.7 mL, 41.8 mmol, 10 eq.) and dimethylaniline (30 mL) in a closed, thick wall glass container was inserted in a salt bath (53% $KNO_3$, 40% $NaNO_2$ and 7% $NaNO_3$, by weight) at 195 $^oC$ until TLC showed no more starting material (approximately 6-7 h). After reaching room temperature, the reaction mixture was partitioned between $Et_2O$ (150 mL) and aqueous 3 M HCl (150 mL); the organic layer was further washed with aqueous 3 M HCl (100 mL), aqueous $NaHCO_3$ (two portions of 120 mL), brine (50 mL) and dried ($Na_2SO_4$). The solvent was removed under reduced pressure to afford a tan oil, which was dissolved in EtOH (20 mL). The resulting solution was cooled to ice bath temperature and treated with aqueous 3 M HCl (2.5 mL). After approximately 10 min., the reaction mixture was diluted with $Et_2O$ (90 mL), washed with aqueous $NaHCO_3$ (two portions of 40 mL), brine (20 mL) and dried ($NaSO_4$). The resulting solution was concentrated under vacuum to approximately 1/5 of its original volume and filtered through a short column of silica gel (hexane:$Et_2O$, 2:1 (v:v)). The title compound was obtained as a pale tan viscous oil (1.25 g, 88%).

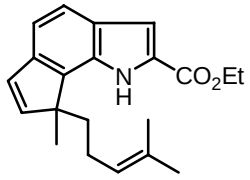
$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.30; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 9.38 (brs, 1 H), 7.41 (d, *J* = 8.5 Hz, 1 H), 7.11 (d, *J* = 2.1 Hz, 1 H), 6.67 (d, *J* = 8.5 Hz, 1 H), 6.57 (dd, *J* = 10.8, 17.8 Hz, 1 H), 5.63 (s, 1 H), 5.43 (d, *J* = 17.8 Hz, 1 H), 5.41 (d, *J* = 10.8 Hz, 1 H), 5.07 (m, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 2.18-1.76 (m, 4 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.44 (s, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ = 162.2, 153.0, 148.7, 137.3, 131.9, 126.1, 124.5, 123.8, 122.1, 114.5, 113.3, 113.1, 108.7, 61.0, 45.5, 39.9, 25.9, 25.6, 24.0, 17.4, 14.7.




**Ethyl 6-(trifluoromethylsulfonyloxy)-7-linalyl-1*H*-indole-2-carboxylate (5.7e)**

To a -30 °C cold solution of ethyl 6-hydroxy-7-linalyl-1*H*-indole-2-carboxylate (**5.7a**) (1.1g, 3.2 mmol, 1.0 eq.) and pyridine (0.39 mL, 4.8 mmol, 1.5 eq.) in $CH_2Cl_2$ (16 mL), was dropwise added over 35 min. a solution of $Tf_2O$ (0.65 mL, 3.9 mmol, 1.2 eq.) in $CH_2Cl_2$ (5.5 mL). The reddish suspension obtained was stirred at -30 °C to -20 °C for 2 h, after which it was allowed to warm up to 0 °C over 1 h, quenched with water (15 mL) and partitioned between aqueous 3 M HCl (100 mL) and $Et_2O$ (150 mL). The organic layer was washed with aqueous 3 M HCl (100 mL), saturated $NaHCO_3$ (two portions of 70 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under vacuum. The deep reddish residue obtained was crudely purified by flash chromatography (hexane:$Et_2O$, 3:1 (v:v); short column; fast elution) affording the title compound as tan oil (1.2 g, 75%).

$R_f$ (hexane: $Et_2O$, 3:1 (v:v)) 0.52; $^1$H-NMR (300 MHz, $CDCl_3$): δ = 9.70 (brs, 1 H), 7.53 (d, *J* = 8.8 Hz, 1 H), 7.08 (d, *J* = 1.8 Hz, 1 H), 7.02 (dd, *J* = 0.4, 8.8 Hz, 1 H), 6.46 (dd, *J* = 10.7, 18.0 Hz, 1H), 5.37 (dd, *J* = 18.0 Hz, 1 H), 5.34 (d, *J* = 10.7 Hz, 1H), 4.90-4.98 (m, 1H), 4.32 (qd, *J* = 0.4, 7.0 Hz, 2H), 1.82-2.10 (m, 4H), 1.64 (s, 3H), 1.54 (s, 3H), 1.35 (s, 3H), 1.33 (td, *J* = 0.4, 7.0 Hz, 3H).




**Ethyl 8-methyl-8-(4-methylpent-3-enyl)-1,8-dihydrocyclopenta[g]indole-2-carboxylate (5.18)**

A mixture of indole (**5.7e**) (50 mg, 0.1 mmol, 1.0 eq.), $Pd(OAc)_2$ (2.5 mg, 0.01 mmol, 10 mol%), $K_2CO_3$ (44 mg, 0.3 mmol, 3.0 eq.), and the dppe (13 mg, 0.03 mmol, 30 mol%) in degassed THF (2.1 mL) was refluxed for 2½ h. After cooling to room temperature, water (2 mL) was added and the mixture was partitioned between $Et_2O$ (15 mL) and water (10 mL). The organic layer was washed with brine (5 mL), dried ($MgSO_4$) and concentrated under vacuum. The obtained residue was purified by flash chromatography (hexane: $Et_2O$, 2:1 (v:v)) to afford the title compound as a faint yellow oil.

$^1$H-NMR (300 MHz, $CDCl_3$): δ = 8.63 (brs, 1 H), 7.58 (dd, *J* = 0.75 Hz, *J* = 8.1 Hz, 1 H), 7.29 (d, *J* = 2.0 Hz, 1 H), 7.19 (d, *J* = 8.1 Hz, 1 H), 6.78 (d, *J* = 5.4 Hz, 1 H), 6.39 (d, *J* = 5.4 Hz, 1 H), 4.94 (m, 1 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 2.1-1.59 (m, 4 H), 1.55 (brs, 3 H), 1.44 (s, 3 H), 1.43 (t, J = 7.1 Hz, 3 H), 1.36 (brs, 3 H). ). $^{13}$C-NMR (75

MHz, $CDCl_3$): $\delta$ = 162.5, 144.7, 141.4, 134.1, 132.7, 131.9, 130.1, 127.6, 126.7, 124.4, 121.4, 116.1, 109.9, 61.2, 54.1, 38.0, 25.8, 23.9, 22.8, 17.7, 14.7.

# Part II

Catalytic Asymmetric Reactions of Enecarbamates with $\alpha,\alpha'$-Dicarbonyl Compounds

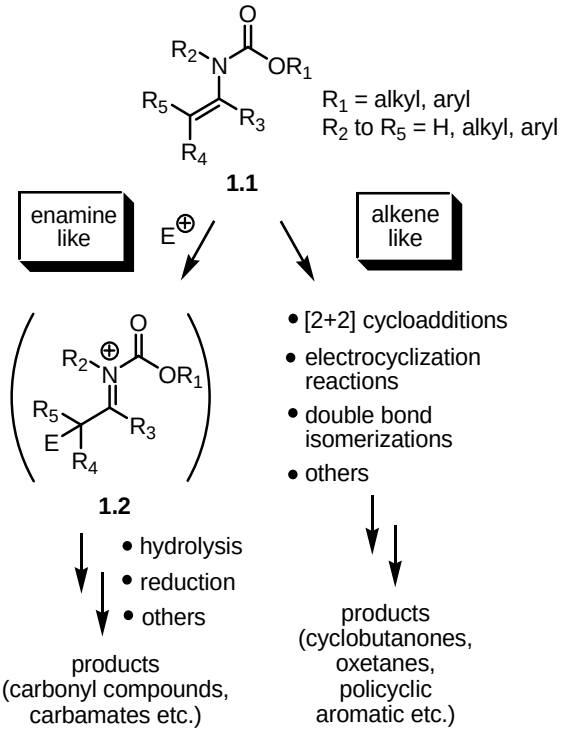
Part II

# CHAPTER 1
# Enecarbamates - An Overview

## 1.1 - Introduction

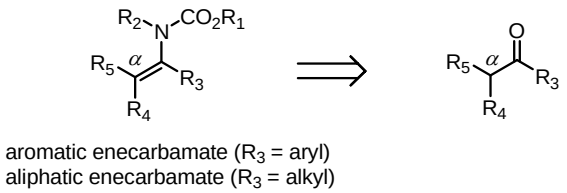
Enecarbamates (**1.1**) are a class of compounds in which a carbon-carbon double bond occurs next to the nitrogen of a carbamate group.

Like the structurally related enamines, enecarbamates can react with electrophiles ($E^+$) at the $\alpha$ position leading to *N*-acyl-iminium ion-type intermediates (**1.2**) which can then be converted to a variety of products.[1.1] On the other hand, enecarbamates can also participate in a range of processes where the carbamate functionality is not directly involved (although it can play a secondary role) and that are more characteristic of isolated carbon-carbon double bonds (Scheme 1.1). Several examples of this double reactivity pattern will be illustrated later (*vide infra*, section 1.2).



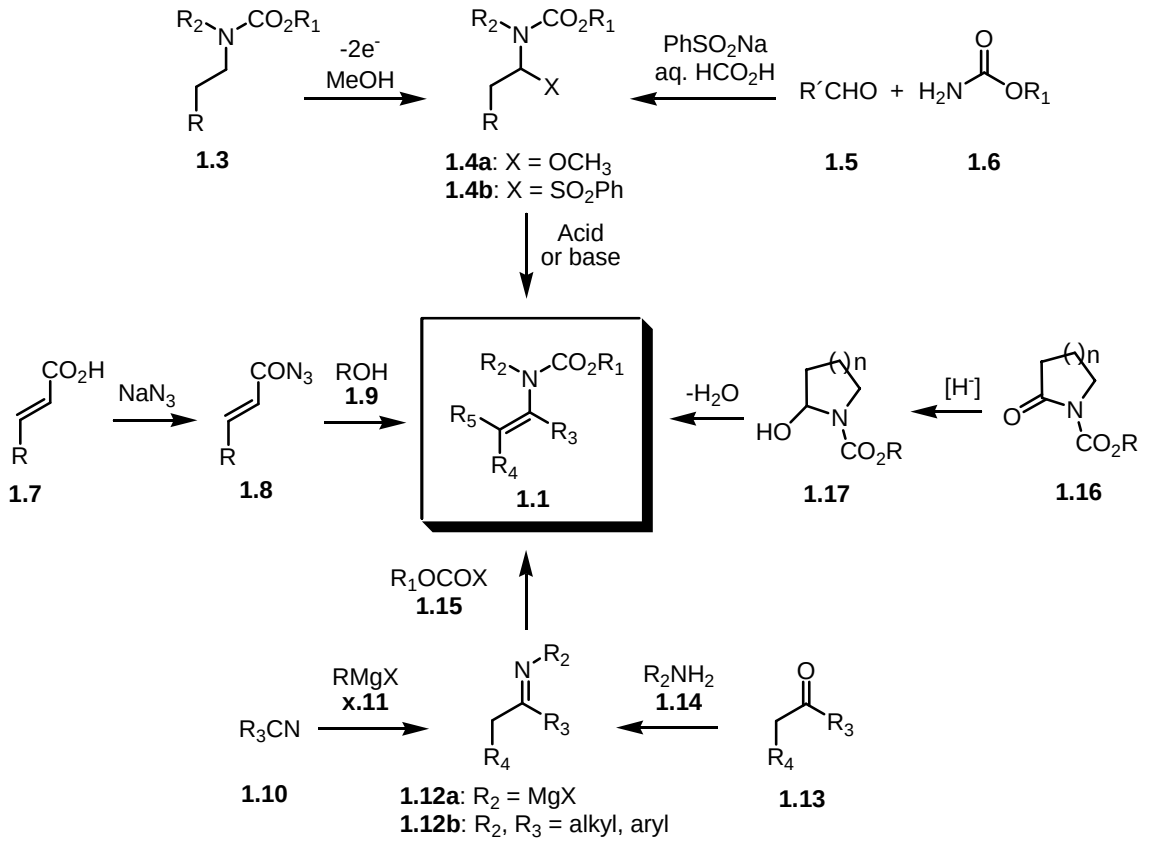

**Scheme 1.1** Typical reactivity pattern of enecarbamates (**1.1**).

[1.1] For the purpose of the present thesis, enecarbamates (**1.1**) will be considered as formal derivatives of the corresponding ketones. Hence, the enecarbamate $\alpha$-position corresponds to the $\alpha$-position of the parent ketone and aromatic/aliphatic enecarbamates refer to those derived from aromatic/aliphatic ketones, respectively (Scheme 1.A).




**Scheme 1.A** Enecarbamates as formal derivatives of ketones.

Enecarbamates (**1.1**) have been prepared by different methods and a representative selection is shown in Scheme 1.2. $\alpha$-Methoxy carbamates (**1.4a**), obtained by anodic methoxylation of the corresponding carbamates (**1.3**), can be converted into enecarbamates by elimination of methanol upon heating in the presence of acid or base.[1.2] A related approach involves the base-assisted elimination of phenylsulfinic acid from $\alpha$-amidoalkylphenyl sulfones (**1.4b**), which are available from the Mannich condensation of aldehydes (**1.5**), carbamates (**1.6**), and the sodium salt of phenylsulfinic acid.[1.3] Enecarbamates have also been obtained *via* the Curtius rearrangement of unsaturated acyl azides (**1.8**) in the presence of an alcohol (**1.9**);[1.4] the former can in turn be prepared from the corresponding carboxylic acid (**1.7**).




**Scheme 1.2** Some preparative methods available for the synthesis of enecarbamates (**1.1**).

[1.2] Shono, T.; Yoshihiro, M.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697.

[1.3] (a) Mecozzi, T.; Petrini, M. *Synlett* **2000**, 73. (b) Engberts, J. B. F. N.; Olijnsma, T.; Strating, J. *Rec. Trav. Chim*. **1966**, *85*, 1211.

[1.4] Overman, L. E.; Taylor, G. F.; Jessup, P. J. *Tetrahedron Lett.* **1976**, *36*, 3089.

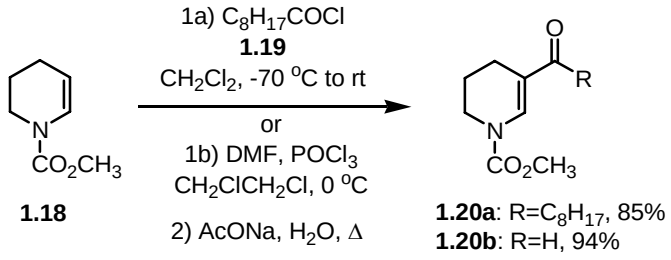
Another route to enecarbamates involves the acylation of intermediates such as metallo-imine (**1.12a**) or imine (**1.12b**) with a formate-type reagent (**1.15**);[1.5] imines (**1.12a**) are typically prepared by addition of a Grignard reagent (**1.11**) to nitriles (**1.10**) whereas imines (**1.12b**) are available *via* condensation of a ketone (**1.13**) with an amine (**1.14**). Finally, endocyclic enecarbamates are available from carbamate-protected lactams (**1.16**) *via* reduction to the parent lactamol (**1.17**) and subsequent dehydration.[1.6]

In spite of the variety of routes available for the preparation of enecarbamates, each one of them has intrinsic limitations either with respect to the accessibility of the required starting material and/or functional group compatibility with the (often harsh) reaction conditions. Furthermore, the stereoselectivity of the process is frequently rather poor and, when efficient, the thermodynamic more stable *E* isomer is often the major product. Thus, it can be argue that the lack of a versatile, high yielding synthesis of enecarbamates is one of the main limitations to a more generalized use of these compounds.

## 1.2 - Uses of Enecarbamates in Organic Synthesis

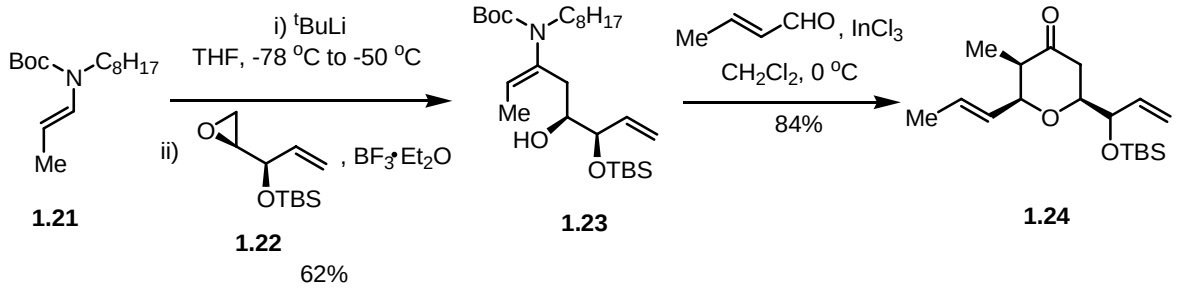
The reduced alkene-nucleophilicity of enecarbamates, a direct consequence of their acylated nature, has to some extent limited their application in thermal carbon-carbon bond forming processes, and until fairly recently their use in organic synthesis was restricted to Friedel-Crafts acylations and Vilsmeier formylations. Two such examples are shown in Scheme 1.3 where the endocyclic enecarbamate (**1.18**) upon treatment with acid chloride (**1.19**) or DMF undergoes acylation or formylation at the $\alpha$-position affording, after treatment with base, the parent carbonyl compounds (**1.20a**) and (**1.20b**), respectively.[1.2]

[1.5] (a) Sven, Y. H.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1965**, *5*, 1454. (b) Chupp, J. C.; Weiss, E. R. *J. Org. Chem.* **1967**, *33*, 2357.
[1.6] (a) Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180. (b) Yu, C.; Hu, L. *Tetrahedron Lett.* **2001**, *42*, 5167.




**Scheme 1.3** Use of enecarbamate (**1.18**) in Friedel-Crafts and Vilsmeyer reactions.

Lately, there has been a growing interest in the use of enecarbamates as carbon nucleophiles, partyl because these compounds have proven to be compatible with *in situ* formation and activation of highly reactive cyclization initiators. A recent example by Funk and Cossey involving an oxocarbenium ion intermediate is shown in Scheme 1.4.[1.7a] Regioselective lithiation of enecarbamate (**1.21**) followed by *in situ* alkylation with chiral epoxide (**1.22**) afforded trisubstituted *E*-enecarbamate (**1.23**) which, upon treatment with crotonaldehyde and $InCl_3$, delivered the all-*cis*-trisubstituted tetrahydropyran-4-one (**1.24**) by means of a diastereoselective Prins cyclisation.



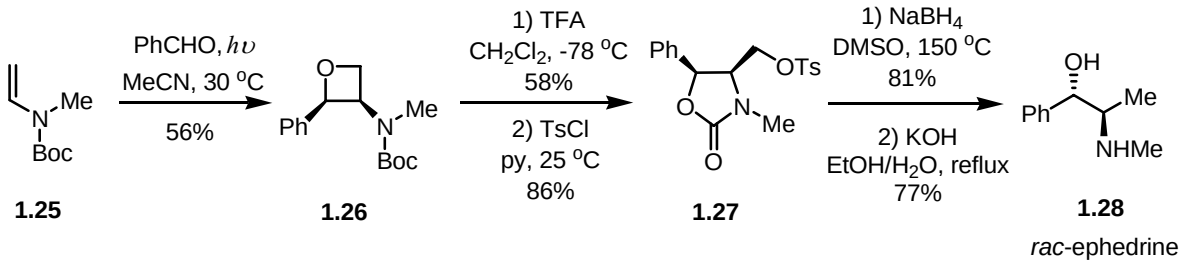

**Scheme 1.4** Use of enecarbamate (**1.23**) in an intramolecular Prins cyclisation.

Enecarbamates have also proved to be excellent substrates for the Paternò-Büchi reaction, particularly with aromatic aldehydes.[1.8] Bach and Schröder reported that the photocyclisation of tertiary enecarbamate (**1.25**) and benzaldehyde proceeded in a regiospecific manner and with good diastereoselectivity to afford the *cis*-amino-

[1.7] (a) Cossey, K., N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216. (b) For a related example where quinone methides are used as cyclisation initiators, see: Angle, S. R.; Arnaiz, D. O.; Boyce, J. P.; Frutos, R. P.; Louie, M. S.; Mattson-Arnaiz, H. L.; Rainier, J. D.; Turnbull, K.; Yang, W. *J. Org. Chem.* **1994**, *59*, 6322.

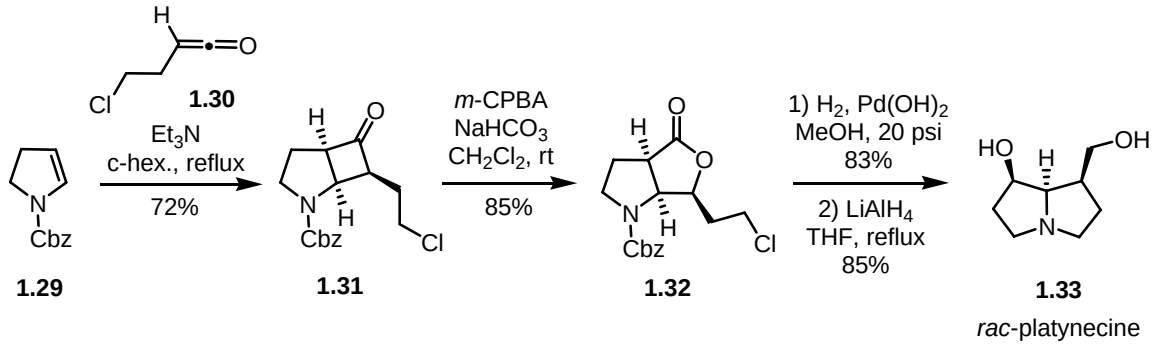
[1.8] (a) Bach, T.; Schröder, J. *J. Org. Chem.* **1999**, *64*, 1265. (b) Bach, T.; Schröder, J. *Synthesis*, **2001**, 1114. (c) Bach, T. *Angew. Chem.* **1996**, *108*, 976.

oxetane (**1.26**) (Scheme 1.5). Upon treatment with TFA oxetane (**1.26**) underwent a ring-expansion to deliver an oxazolidinone ring system which was then converted into the corresponding tosylate (**1.27**). Subsequent reductive dehydrotosylation followed by basic hydrolysis delivered *rac*-ephedrine (**1.28**).[1.8a]




**Scheme 1.5** Use of enecarbamate (**1.25**) in a Paternò-Büchi reaction.

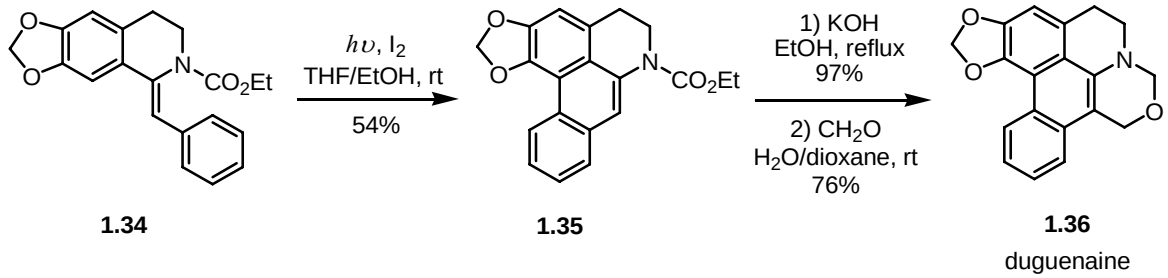
Endocyclic enecarbamates have been employed as ketophiles in [2+2] cycloadditions with free ketenes to deliver functionalized cyclobutanones.[1.9] Correia and co-workers reported that the reaction of enecarbamate (**1.29**) with ketene (**1.30**) affords the *endo*-azabicyclic cyclobutanone (**1.31**) regiospecifically. Upon treatment with *m*-CPBA, the latter undergoes a regioselective Baeyer-Villiger ring expansion to γ-lactone (**1.32**). Subsequent hydrogenolysis of the Cbz protective group followed by reduction of the lactone ring delivered *rac*-platynecine (**1.33**) (Scheme 1.6).[1.9a]




**Scheme 1.6** Total synthesis of *rac*-platynecine (**1.33**) using the [2+2] cycloaddition of enecarbamate (**1.29**) with ketene (**1.30**) as the key step.

[1.9] (a) de Faria, A. R.; Salvador, E. L.; Correia, C. R. D. *J. Org. Chem.* **2002**, *67*, 3651. (b) Miranda, P. C. M. L.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 7735.

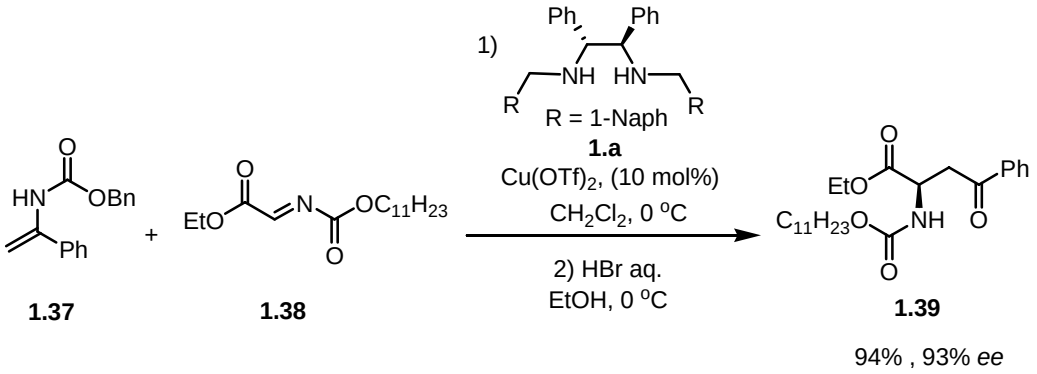
Enecarbamates have also been extensively used in photochemical electrocyclization reactions, notably for the preparation of polycyclic aromatic compounds.[1.10] Lenz and Koszyk used such a reaction in the total synthesis of duguenaine (**1.36**) (Scheme 1.7).[1.11] Irradiation of tetrahydroisoquinoline (**1.34**) in the presence of iodine affords *N*-carbethoxynorneolitsine (**1.35**) by means of a sequence that includes the *cis-trans* isomerisation of the enecarbamate double bond, an electrocyclization reaction and an oxidative re-aromatization. Saponification of the carbamate moiety followed by double condensation with formaldehyde finally delivers duguenaine (**1.36**).




**Scheme 1.7** Total synthesis of duguenaine (**1.36**) from enecarbamate (**1.34**) by means of a tandem *cis-trans* isomerization/electrocyclization/aromatization sequence.

Recently Kobayashi and co-workers reported the first examples of the use of enecarbamates as carbon nucleophiles in asymmetric catalysis.[1.12] In the presence of a catalyst derived from $Cu(OTf)_2$ and the $C_2$-symmetric diamine (**1.a**), secondary enecarbamates such as (**1.37**) added to the double activated imine (**1.38**) affording, after acidic hydrolysis, the $\beta$-keto carbamate (**1.39**) in excellent yield and high enantioselectivity (Scheme 1.8).

[1.10] For reviews see: (a) Lenz, G. R. *Synthesis* **1978**, 489. (b) Campbell, A. L.; Lenz, G. *Synthesis* **1987**, 421. Note: in these reviews no distinction is made between enecarbamates and enamides.
[1.11] Lenz, G. R.; Koszyk, F. J. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1273.
[1.12] Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1679.

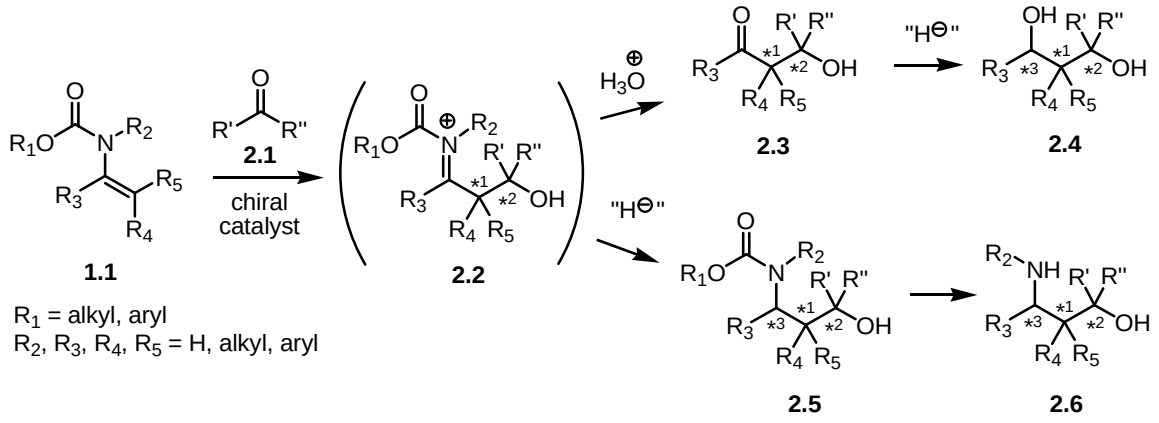



**Scheme 1.8** Use of enecarbamate (**1.37**) as carbon nucleophile in asymmetric catalysis.

# CHAPTER 2
# Aim of the Project

The good results obtained with the catalytic asymmetric addition reaction of enecarbamates to imines[2.1] (*vide* section 1.2, Chapter 1) prompted us to investigate the corresponding reaction with carbonyl compounds.

The catalytic asymmetric addition reaction of enecarbamates (**1.1**) to aldehydes/ketones (**2.1**), if successful, would provide an entry to a range of important 1,3-bifunctional chiral compounds, obtainable by intercepting the chiral *N*-acyl-iminium ion-type intermediate (**2.2**) using different conditions. Accordingly, hydrolysis of (**2.2**) would afford *β*-hydroxy ketones (**2.3**) which could then be reduced to the parent 1,3-diols (**2.4**); on the other hand, direct reduction of the imino linkage in (**2.2**) would allow access to *β*-hydroxy carbamates (**2.5**), which can be viewed as masked 1,3-amino alcohols (**2.6**). Furthermore, the chiral center(s) formed during the catalytic asymmetric step (*1 and *2) could be used to control the configuration at the keto/imino position (*3) upon reduction by means of 1,2- and/or 1,3-chiral induction and thus up to three contiguous chiral centers could in principle be constructed (Scheme 2.1).[2.2]




**Scheme 2.1** Aimed catalytic asymmetric addition reaction of enecarbamates (**1.1**) to aldehydes/ketones (**2.1**) and the 1,3-bifunctional products that can be obtained.

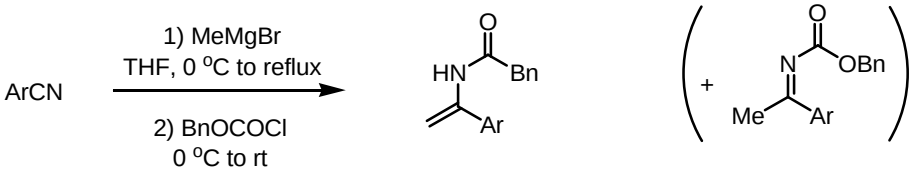
[2.1] Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1679.

[2.2] For a general review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

# CHAPTER 3
# Preparation of Enecarbamates and Chiral Ligands[3.1]

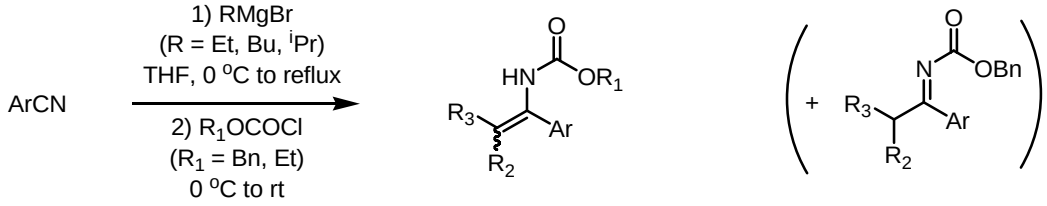
## 3.1 - Preparation of Enecarbamates

The enecarbamates used through out this work were prepared by two different methods, depending on their substitution pattern. Aromatic enecarbamates (*i.e.*, those with an aryl moiety at the same carbon as the carbamate group) were obtained *via* addition of a Grignard reagent to an aromatic nitrile and subsequent trapping of the metallo-imine intermediate with a chloroformate reagent (one pot) (Scheme 3.1).[3.2]




**1.37**: Ar = Ph, 48%
**3.1**: Ar = *p*-OMePh, 43%
**3.2**: Ar = *p*-ClPh, 47%
**3.3**: Ar = *p*-MePh
**3.4**: Ar = 2-Nap

**3.5**




**3.6**: Ar = Ph, $R_1$ = Bn, $R_2$ = Me, $R_3$ = H,
31% *E* plus 14% *Z*
**3.7**: Ar = *p*-OMePh, $R_1$ = Bn, $R_2$ = Me, $R_3$ = H,
33% *E* plus 9% *Z*
**3.8**: Ar = *p*-ClPh, $R_1$ = Bn, $R_2$ = Me, $R_3$ = H,
33% *E* plus 12% *Z*
**3.9**: Ar =*p*-OMePh, $R_1$ = Et, $R_2$ = Me, $R_3$ = H,
24% *E* plus 9% *Z*
**3.10**: Ar = Ph, $R_1$ = Bn, $R_2$ = $R_3$ = Me
**3.11** : Ar = Ph, $R_1$ = Bn, $R_2$ = Et, $R_3$ = H

**3.12**

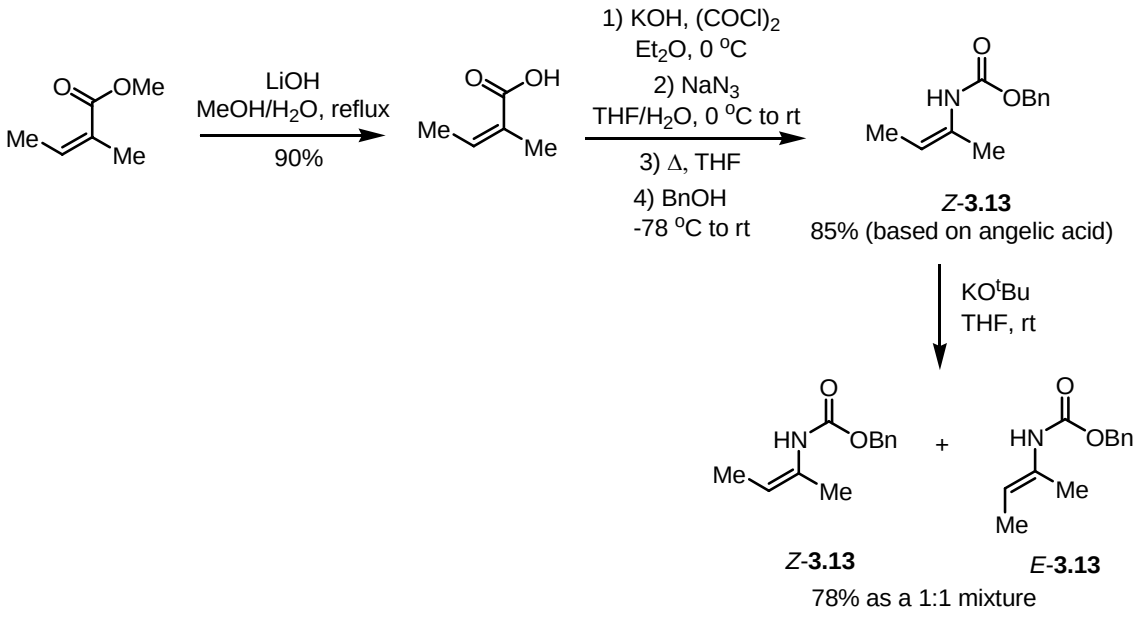
**Scheme 3.1** Preparation of aromatic enecarbamates (**1.37**), (**3.1**) to (**3.4**) and (**3.6**) to (**3.11**).

[3.1] Some of the enecarbamates and chiral ligands described in this chapter and used occasionally during this work were available "on the shelf" in the Koyahashi's group; for these no yields are reported.

[3.2] Sven, Y. H.; Kagan, H. B. *Bull Soc. Chim. Fr.* **1965**, *5*, 1454.

The enecarbamates thus obtained were isolated in moderate yields (typically around 40%) by standard column flash chromatography; imines of the type (**3.5**) and (**3.12**) were common by-products. In those cases where *E*/*Z* isomerism is possible (*i.e.*, for enecarbamates (**3.6**) to (**3.11**)), a mixture of isomers was always obtained and a modest *E*-selectivity was observed. The two geometric isomers could be separated by careful flash chromatography.

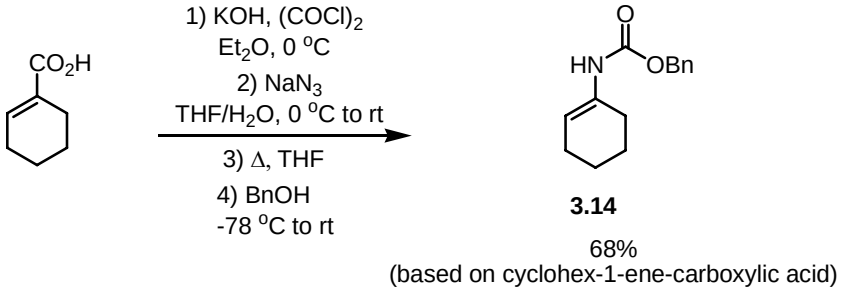
On the other hand, aliphatic enecarbamates (*i.e.*, those containing an alkyl group at the same carbon as the carbamate moiety) were prepared from the corresponding *α,β*-unsaturated acid chlorides using the Curtius rearrangement to access the carbamate functionality.[3.3] Angelic acid methyl ester was first hydrolyzed with LiOH to afford angelic acid (90% yield) which was converted into its acid chloride by treatment with oxalyl chloride; subsequent reaction with $NaN_3$ afforded the corresponding acyl azide which was thermolysed into the parent isocyanate; reaction with BnOH then delivered *Z*-(**3.13**) in high yield (85% based on the angelic acid). The latter, upon treatment with $KO^tBu$, afforded a 1:1 mixture of the both *E* and *Z* isomers which could be separated by careful preparative thin-layer chromatography (PTLC) (Scheme 3.2).




**Scheme 3.2** Preparation of aliphatic enecarbamates *Z*- and *E*-(**3.13**).

[3.3] Overman, L.E.; Taylor, G. F.; Jessup, P. J. *Tetrahedron Lett.* **1976**, *36*, 3089.

The cyclohexyl-derived enecarbamate (**3.14**) was prepared in a similar manner from cyclohex-1-ene carboxylic acid (Scheme 3.3).

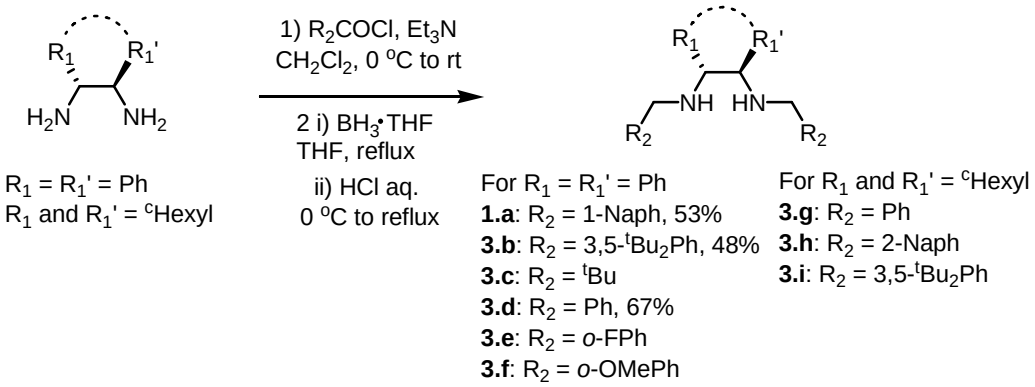



**Scheme 3.3** Preparation of aliphatic enecarbamate (**3.14**).

Notably, all the enecarbamates are solid/crystalline materials which could be stored at room temperature for a long period of time without special precautions.

## 3.2 - Preparation of Chiral Ligands

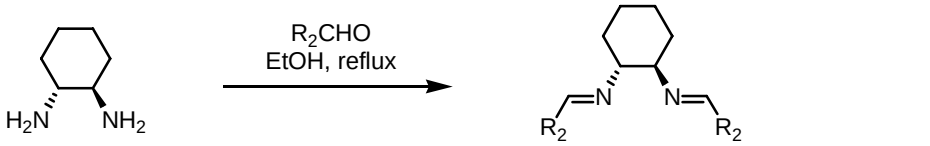
The chiral ligands used in these studies were mainly bidentate, $C_2$-symmetric diamines and diimines prepared from (*R*,*R*)-1,2-diphenyl-1,2-diaminoethane and (1*R*,2*R*)-cyclohexanediamine. The diamine ligands (**1.a**) and (**3.b**) to (**3.i**) were obtained *via* reaction of the starting diamine with the appropriated acid chloride followed by borane reduction (Scheme 3.4).[3.4]




**Scheme 3.4** Preparation of the chiral diamine ligands (**1.a**) and (**3.b**) to (**3.i**).

[3.4] Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507 and references therein.

The diimines ligands (**3.j**) to (**3.u**) were prepared by reaction of (1*R*,2*R*)-cyclohexanediamine with the appropriate aldehyde in refluxing EtOH.[3.5,3.6]

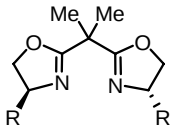



**3.j**: $R_2$ = Ph, 85%
**3.k**: $R_2$ = 1-Naph
**3.l**: $R_2$ = 2-Naph
**3.m**: $R_2$ = 3,5-$^t$Bu$_2$Ph
**3.n**: $R_2$ = *o*-Tol
**3.o**: $R_2$ = *p*-Tol
**3.p**: $R_2$ = 2-Naph
**3.q**: $R_2$ = *p*-EtPh
**3.r**: $R_2$ = *p*-iPrPh
**3.s**: $R_2$ = *p*-FPh
**3.t**: $R_2$ = *p*-ClPh
**3.u**: $R_2$ = *p*-BrPh, 91%

**Scheme 3.5** Preparation of the chiral diimines ligands (**3.j**) to (**3.u**).

[3.5] Hesemann, P.; Moreau, J. J. E.; Soto, T. *Synth. Comm.* **2003**, *33*, 183.

[3.6] In addition to the previously described diamine and diimine ligands, the commercially available oxazolidines (**3.v**) and (**3.x**) were also used in this work (Figure 3.A).




**3.v**: R = Ph
**3.x**: R = $^t$Bu

**Figure 3.A** Commercially available oxazolidines ligands (**3.v**) and (**3.x**).

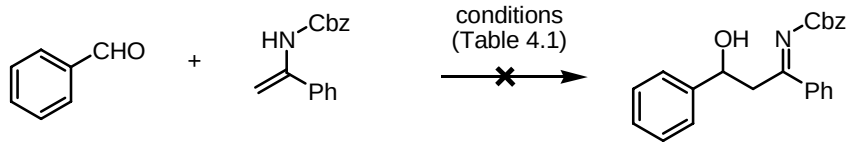
# CHAPTER 4
# Results and Discussion

## 4.1 - Addition of Enecarbamates to Aldehydes

### 4.1.1 - Use of Benzaldehydes as Substrates

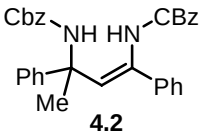
Regarding the addition reaction of enecarbamates to aldehydes, the initial studies were performed with benzaldehyde and enecarbamate (**1.37**) (Table 4.1).

**Table 4.1** (Attempted) reaction of enecarbamate (**1.37**) with benzaldehyde.

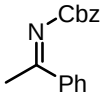



**1.37** **4.1**

| Entry[a] | L.A.[b] | Additive (eq.)[b] | TLC observations[c] |
|---|---|---|---|
| 1 | - | - | SMs |
| 2[d] | $Cu(OTf)_2$ | - | SMs, **4.2** and **4.3** |
| 3 | $Yb(OTf)_3$ | - | SMs, **4.2** and **4.3** |
| 4 | $Sc(OTf)_3$ | - | SMs, **4.2** and **4.3** |
| 5[e] | - | $Et_3N$ (1.2) | SMs and **4.3** |
| 6[f] | - | DMF (3.0) | SMs and **4.3** |




**4.2**



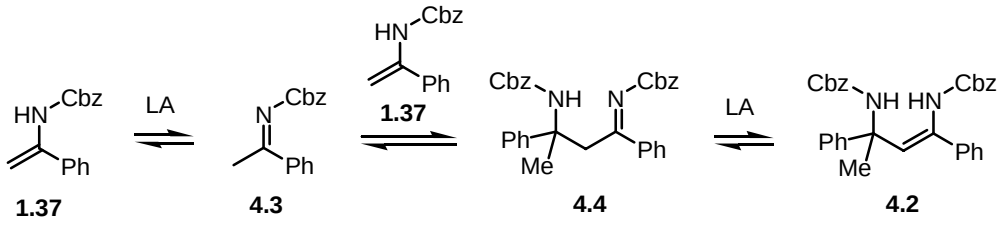

**4.3**

[a] The reactions were performed in $CH_2Cl_2$ at 0 °C to rt with 10 mol% of the catalyst, 1.0 eq. of benzaldehyde and 1.5 eq. of enecarbamate (**1.37**), unless otherwise stated;
[b] "-" stands for "not used";
[c] As judged by TLC at the end of the reaction;
[d] The homocoupling enecarbamate (**4.2**) and the Cbz-protected imine (**4.3**) were isolated in 28% and 13% yields, respectively.

As it can be seen, the reaction did not proceed in the absence of a catalyst or an additive (entry 1, Table 4.1). On the other hand, the use of a catalytic amount of $Cu(OTf)_2$, which was expected to enhance the electrophilicity of the benzaldehyde, resulted in the isolation of the homocoupling enecarbamate (**4.2**) and the Cbz-imine

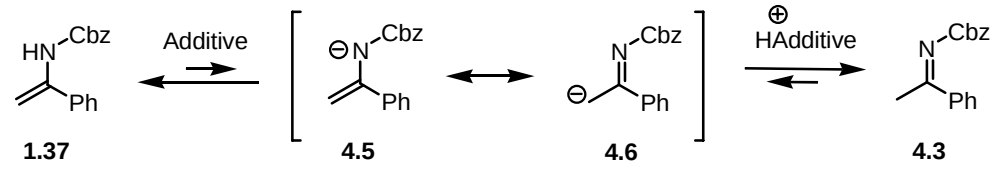
(**4.3**) in 28% and 13% yields, respectively (entry 2, Table 4.1). The use $Yb(OTf)_3$ and $Sc(OTf)_3$ resulted in similar observations (entry 3 & 4, respectively, Table 4.1).

The formation of the enecarbamate (**4.2**) and imine (**4.3**) is most likely a direct consequence of the Lewis acidic sensitivity of enecarbamates and it was rationalized by the sequence shown in Scheme 4.1.




**Scheme 4.1** LA-promoted formation of Cbz-imine (**4.3**) and homocoupled enecarbamate (**4.2**).

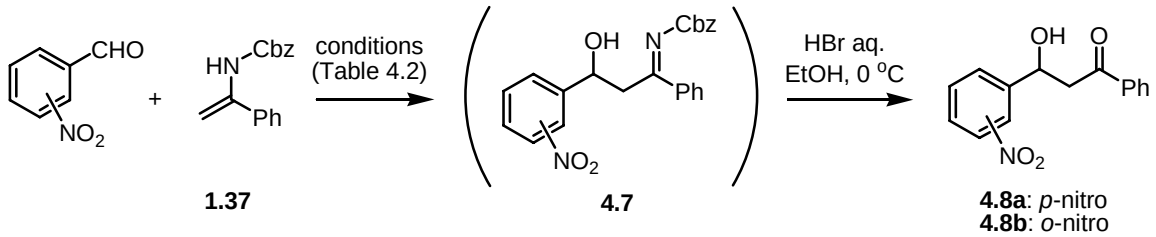
Entries 5 and 6 in Table 4.1, where base-like additives such as $Et_3N$ and DMF were added, represent a conceptually different approach to promote the reaction in that it was the nucleophilicity of the enecarbamate (**1.37**) that was attempted to be enhanced. The idea behind the use of such additives was to form, even if in a small amount, the anionic species (**4.5**), which was expected to be a better nucleophile than enecarbamate (**1.37**). Disappointingly, however, this only promoted the formation of the Cbz-protected imine (**4.3**), presumably as a result of the ambidentate nature of (**4.5**) (Scheme 4.2).




**Scheme 4.2** Base-promoted formation of Cbz-imine (**4.3**).

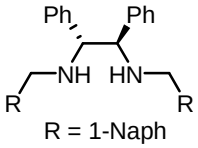
To counteract the weak nucleophilicity of enecarbamate (**1.37**), which is a general feature of this class of compounds, it was decided to use a more electrophilic substrate than benzaldehyde and nitro-benzaldehydes were chosen (Table 4.2).

**Table 4.2** Reaction of enecarbamate (**1.37**) with nitrobenzaldehydes.




**1.37** **4.7** **4.8a**: *p*-nitro **4.8b**: *o*-nitro

| Entry[a] | Aldehyde | Catalyst[b] | Yield (%) | TLC observations[c] |
|---|---|---|---|---|
| 1 | *p*-$NO_2$PhCHO | - | 0 | SMs |
| 2[d] | | - | 0 | SMs |
| 3[e] | | $Cu(OTf)_2$ | 0 | SMs, **4.2** and **4.3** |
| 4 | | $Sc(OTf)_3$ | 0 | SMs, **4.2** and **4.3** |
| 5 | | $Yb(OTf)_3$ | 0 | SMs, **4.2** and **4.3** |
| 6 | | $Mg(OTf)_2$ | 0 | SMs, **4.2** and **4.3** |
| 7 | | $Ce(OTf)_3$ | 0 | SMs, **4.2** and **4.3** |
| 8[e] | | $BF_3{\cdot}Et_2O$ | 8 | SMs, **4.2** and **4.3** |
| 9[f] | | $Cu(OTf)_2$ + **1.a** | 9 | SMs and ***minor* 4.3** |
| 10[e] | *o*-$NO_2$PhCHO | $BF_3{\cdot}Et_2O$ | 16 | SMs, **4.2** and **4.3** |
| 11[g] | | $Cu(OTf)_2$ + **1.a** | 15 | SMs and ***minor* 4.3** |




R = 1-Naph

**1.a**

[a] The reactions were performed in $CH_2Cl_2$ at 0 °C to rt with 10 mol% of the catalyst, 1.0 eq. of the nitrobenzaldehyde and 1.5 eq. of enecarbamate (**1.37**), unless otherwise stated;

[b] "-" stands for "not used";

[c] As judged by TLC at the end of the reaction or, for entries 8 to 11, before the acidic hydrolysis;

[d] The reaction was performed at reflux;

[e] A stoichiometric amount of $BF_3{\cdot}Et_2O$ was used;

[f] The *β*-hydroxy ketone (**4.8a**) was obtained with 36% *ee*.

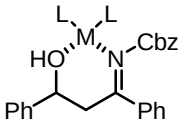
[g] The *ee* of *β*-hydroxy ketone (**4.8b**) was not determined.

Initially *p*-nitrobenzaldehyde was used. In the absence of a catalyst, either at room temperature or at reflux, the reaction did not proceed and both SMs remained unchanged (entries 1 & 2, Table 4.2, respectively). The use of several LA as catalysts, namely $Cu(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Mg(OTf)_2$ and $Ce(OTf)_3$ resulted in the formation of dimeric enecarbamate (**4.2**) and Cbz-imine (**4.3**) (entries 3 to 7, Table 4.2, respectively). On the other hand, in the presence of a stoichiometric amount of

$BF_3 \cdot Et_2O$ and after acidic hydrolysis,[4.1] the expected *β*-hydroxy ketone (**4.8a**) was isolated, albeit in very poor yield (8%) (entry 8, Table 4.2). An important observation was made when a combination of $Cu(OTf)_2$ and chiral diamine (**1.a**) was used (entry 9, Table 4.2). While the reaction only delivered a 9% yield of the desired *β*-hydroxy ketone (**4.8a**), no formation of the dimeric enecarbamate (**4.2**) occurred and the Cbz-imine (**4.3**) was present in only a very small amount, as judged by TLC. Thus, under these conditions the starting enecarbamate (**1.37**) is stable. A similar result was obtained when the same $Cu(OTf)_2$-diamine (**1.a**) combination was used with *o*-nitrobenzaldehyde; the expected *β*-hydroxy ketone (**4.8b**) was formed in a slightly higher yield (15%) and only a very small amount of the Cbz-imine (**4.3**) was observed by TLC plate (entry 11, Table 4.2).

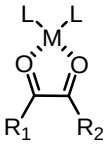
## 4.1.2 - Use of Ethyl Glyoxylate as the Substrate

The yields obtained for the formation of *β*-hydroxy ketones (**4.8a**) and (**4.8b**) (*vide supra*, Table 4.2) correspond in good approximation to the amount of the catalyst used. This observation was rationalized by considering that the initial product, *β*-hydroxy imine (**4.7**), irreversibly traps the catalyst (as in (**4.9**)). This problem was addressed by the use of *α,α'*-dicarbonyl compounds, which besides being highly reactive, are known to efficiently form five-membered chelate species (**4.10**) with transition metals (Figure 4.1).[4.2]




**4.9**

*vs.*




**4.10**

**Figure 4.1**

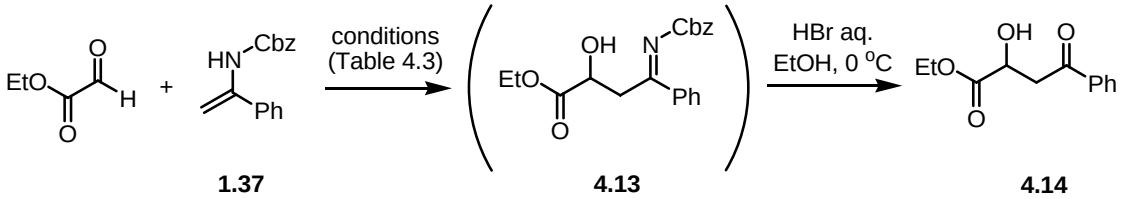
[4.1] The hydrolysis procedure facilitates the isolation and analysis of the reaction products and it will be used extensively in this work.

[4.2] For selected examples of the use of *α,α'*-dicarbonyl compounds in asymmetric catalysis, see: (a) aldol reactions with pyruvate esters: i) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893; ii) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686. (b) carbonly-ene reactions with ethyl glyoxylate: Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824. (c) hetero-Diels-Alder reactions with *α*-keto ester heterodienes: i) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3372. ii) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2404.

### 4.1.2.1 - Catalyzed Addition Reaction of Enecarbamates to Ethyl Glyoxylate

The reaction of enecarbamate (**1.37**) with ethyl glyoxylate,[4.3] the simplest of the *α,α'*-dicarbonyl compounds, was investigated (Table 4.3). Initially, we concentrated on the feasibility of the process rather than its enantioselectivity.

**Table 4.3** Reaction of enecarbamate (**1.37**) with ethyl glyoxylate - I.




**1.37** **4.13** **4.14**

| Entry[a] | Catalyst[b] | Yield (%) | TLC observations[c] |
|---|---|---|---|
| 1 | - | 13 | **1.37** |
| 2 | $Cu(OTf)_2$ | 18 | **4.2** and **4.3** |
| 3 | $CuClO_4 \cdot 4CH_3CN$ | 67 | **4.2** and **4.3** |
| 4 | $Sc(OTf)_3$ | 40 | **4.2** and **4.3** |
| 5 | $Yb(OTf)_3$ | 59 | **4.2** and **4.3** |
| 6 | $Ni(OTf)_2$ | <58 | **4.2** and **4.3** |
| 7[d] | $Cu(OTf)_2$ + **1.a** | 93 | - |

[a] The reactions were performed in $CH_2Cl_2$ at 0 °C with 10 mol% of the catalyst, 1.0 eq. of enecarbamate (**1.37**) and 1.2 eq. of ethyl glyoxylate, and subjected to acidic hydrolysis after 1 h, unless otherwise stated;
[b] "-" stands for "not used";
[c] As judged by TLC before the acidic hydrolysis;
[d] The *β*-hydroxy ketone (**4.14**) was obtained with 55% *ee*.

Even in the absence of any catalyst the reaction afforded the expected *β*-hydroxy ketone (**4.14**) in 13% yield after acid hydrolysis (entry 1, Table 4.3). The catalytic use of several LA, namely $Cu(OTf)_2$, $CuClO_4 \cdot 4CH_3CN$, $Sc(OTf)_3$, $Yb(OTf)_3$ and $Ni(OTf)_2$, also delivered the desired product in yields ranging 18-67% but extensive conversion of the starting enecarbamate (**1.37**) into the homocoupled enecarbamate (**4.2**) and the Cbz-protected imine (**4.3**) occurred (entries 2 to 6, Table 4.3). The best

[4.3] Ethyl glyoxylate is commercially available as a solution of the corresponding polymer. After removal of the solvent, monomeric ethyl glyoxylate is obtained by distillation of the polymeric residue with a catalytic amount of $P_2O_5$.

result was obtained when the catalyst prepared from $Cu(OTf)_2$ and the $C_2$-symmetric diamine (**1.a**) was used (93% yield, entry 7, Table 4.3). Formation of (**4.2**) and (**4.3**) was not observed under these conditions which can be ascribed to a *decrease in the Lewis acidity of the copper ion when coordinated to the diamine ligand (**1.a**)*.

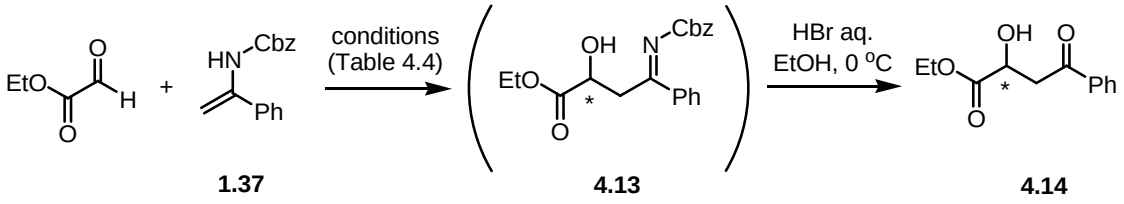
### 4.1.2.2 - Enantioselective Catalyzed Addition Reaction of Enecarbamates to Ethyl Glyoxylate

Having established the feasibility of the reaction of enecarbamates with ethyl glyoxylate to afford $\beta$-hydroxy ketones, the extension to an enantioselective version of this process was next investigated.

#### 4.1.2.2.1 - General Screening of Catalysts

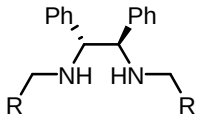
A preliminary screening was conducted where various LA/$C_2$-symmetric chiral ligands combinations were tested. The results are shown in Table 4.4.

**Table 4.4** Reaction of enecarbamate (**1.37**) with ethyl glyoxylate - II.

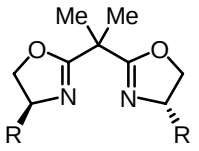



**1.37** **4.13** **4.14**

| Entry[a] | L.A. | Chiral Ligand | Yield (%) | *ee* (%) |
|---|---|---|---|---|
| 1 | $LiClO_4$ | **3.d** | 21 | 0 |
| 2 | NaOTf | **3.d** | trace | nd |
| 3 | $Mg(OTf)_2$ | **3.b** | 5 | 38 |
| 4[b] | $Sc(OTf)_3$ | **3.d** | 58 | 28 |
| 5[b,c] | $Sc(OTf)_3$ | **3.d** | 40 | 17 |
| 6[b] | $Sc(OTf)_3$ | **3.x** | 60 | 1 |
| 7[d] | $FeCl_2$ | **3.d** | <38 | 2 |
| 8[b,e] | $CoCl_2$ | **3.d** | 77 | 2 |
| 9[b,e] | $CoCl_2$ | **3.x** | 73 | 1 |
| 10 | $Ni(OTf)_2$ | **3.d** | 87 | 56 |
| 11 | $Cu(OTf)_2$ | **1.a** | 93 | 55 |



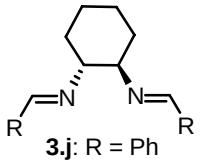

**1.a**: R = 1-Naph
**3.b**: R = 3,5-$^t$Bu$_2$Ph
**3.d**: R = Ph



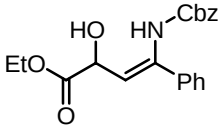

**3.x**: R = $^t$Bu

**Table 4.4** (*cont.*)

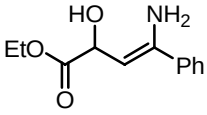
| Entry[a] | L.A. | Chiral Ligand | Yield (%) | *ee* (%) |
|---|---|---|---|---|
| 12 | $CuClO_4 \cdot 4CH_3CN$ | **1.a** | 90 | 35 |
| 13 | $Zn(OTf)_2$ | **1.a** | 86 | 39 |
| 14 | $Zn(OTf)_2$ | **3.i** | 62 | 16 |
| 15[d] | $AgSbF_6$ | **3.j** | <14 | 18 |
| 16 | AgOTf | **3.j** | <31 | 35 |
| 17 | $Sn(OTf)_2$ | **3.d** | 44 | 8 |
| 18[b,e] | $BiCl_3$ | **3.d** | <26 | 2 |
| 19 | $La(OTf)_3$ | **3.d** | 70 | 0 |
| 20 | $Ce(OTf)_3$ | **3.d** | 68 | 0 |
| 21 | $Pr(OTf)_3$ | **3.d** | 61 | 0 |
| 22 | $Nd(OTf)_3$ | **3.d** | 74 | 2 |
| 23 | $Sm(OTf)_3$ | **3.d** | 82 | 0 |
| 24 | $Sm(OTf)_3$ | **3.j** | 65 | 2 |
| 25 | $Sm(OTf)_3$ | **3.x** | 88 | 0 |
| 26 | $Ho(OTf)_3$ | **3.d** | 66 | 0 |
| 27 | $Yb(OTf)_3$ | **3.b** | 40 | 2 |



**3.j**: R = Ph



**4.15**

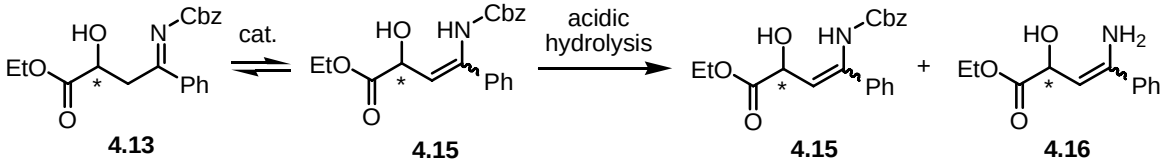


**4.16**

[a] The reactions were performed in $CH_2Cl_2$ at 0 °C with 10 mol% of the catalyst, 1.0 eq. of enecarbamate (**1.37**) and 1.2 eq. of ethyl glyoxylate and subjected to acidic hydrolysis after 1 h, unless otherwise stated;
[b] Enecarbamate homocoupled product (**4.2**) and Cbz-imine (**4.3**) observed on TLC;
[c] The reaction was performed at rt;
[d] The isolated product was not completely pure;
[e] The *β*-hydroxy enecarbamate (**4.15**) and *β*-hydroxy enamine (**4.16**) were formed.

From these studies it emerged that copper(I), copper(II) and nickel(II) salts have the best catalytic activity for this reaction, affording the aldol-type product (**4.14**) in higher than 90% yield (entry 10 for $Ni(OTf)_2$; entries 11 & 12 for $Cu(OTf)_2$ and $CuClO_4 \cdot 4CH_3CN$, Table 4.4, respectively) and with enantiomeric excesses as high as 56% (entry 10 for $Ni(OTf)_2$, Table 4.4). On the other hand, lithium(I), sodium(I), magnesium(II), iron(II), silver(I), and bismuth(III) do not seem to be efficient catalyst for this reaction (entries 1, 2, 3, 7, 15 & 16 and 18, Table 4.4, respectively). When the reaction was performed with scandium(III), cobalt(II) and bismuth(III) salts (entries 4 to 6, 8 & 9 and 18, Table 4.4, respectively), the dimeric enecarbamate (**4.2**) was observed on TLC. Furthermore, the *β*-hydroxy enecarbamate (**4.15**) and the corresponding enamine (**4.16**) were also isolated or detected by TLC for these cases. These results imply that, under these stronger Lewis acidic conditions, the

intermediate *β*-hydroxy imine (**4.13**) is not stable and it isomerizes to the corresponding enecarbamate (**4.15**); acidic hydrolysis then partially removes the Cbz group delivering the starting *β*-hydroxy enecarbamate (**4.15**) and the *β*-hydroxy enamine (**4.16**) (Scheme 4.3).




**4.13** **4.15** **4.15** **4.16**

**Scheme 4.3** L.A.-promoted formation of *β*-hydroxy enecarbamate (**4.15**) and enamine (**4.16**).

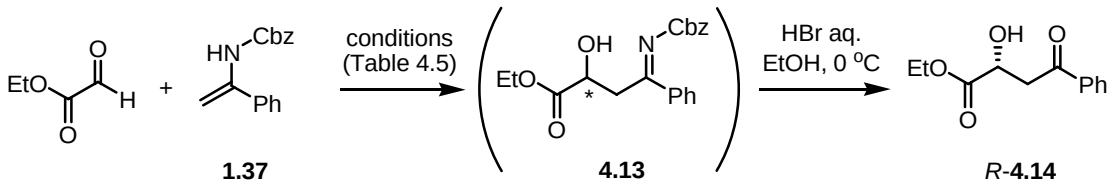
Finally, when different lanthanide salts were used the desired product was produced in modest to good yields (40% to 88%), but with negligible enantiomeric excesses (<6%) (entries 19 to 27, Table 4.4).

The good results obtained with the cooper and nickel salts prompted us to screen these metals more carefully.

### 4.1.2.2.2 - Use of Copper(II)-Based Catalysts

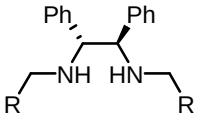
We started with copper(II) and the results are shown in Table 4.5.

**Table 4.5** Reaction of enecarbamate (**1.37**) with ethyl glyoxylate using Cu(II)-based catalysts.




**1.37** **4.13** ***R*-4.14**

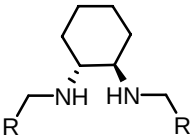
| Entry[a] | L.A. | Chiral Ligand | Yield (%) | *ee* (%)[b] |
|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | **1.a** | 93 | 55 |
| 2[c] | | **1.a** | 91 | 54 |
| 3[d] | | **1.a** | 89 | 58 |
| 4 | | **3.b** | 74 | 59 |
| 5[e] | | **3.b** | 44 | 47 |
| 6 | | **3.c** | 58 | 57 |



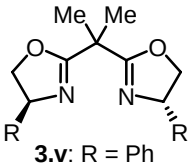

**1.a**: R =1-Naph
**3.b**: R = 3,5-$^{t}Bu_2$Ph
**3.c**: R = $^{t}$Bu
**3.d**: R = Ph
**3.e**: R = *o*-FPh
**3.f**: R = *o*-OMePh

**Table 4.5** (*cont.*)

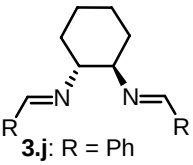
| Entry[a] | L.A. | Chiral Ligand | Yield (%) | *ee* (%)[b] |
|---|---|---|---|---|
| 7 | $Cu(OTf)_2$ | **3.d** | 96 | 46 |
| 8 | | **3.e** | 97 | 37 |
| 9 | | **3.f** | 94 | 31 |
| 10[b] | | **3.v** | 85 | 31 |
| 11[b,d] | | **3.v** | 91 | 31 |
| 12[b] | | **3.x** | 70 | 73 |
| 13 | | **3.j** | 65 | 70 |
| 14 | | **3.k** | 66 | 28 |
| 15 | | **3.l** | 71 | 52 |
| 16 | | **3.m** | 68 | 17 |
| 17 | | **3.g** | 89 | 51 |
| 18 | | **3.h** | 91 | 50 |
| 19 | | **3.i** | quant. | 62 |
| 20[b] | $CuCl_2$ | **1.a** | 47 | 17 |
| 21 | | **3.b** | 55 | 26 |
| 22 | | **3.j** | 50 | 19 |
| 23 | $Cu(SbF_6)_2$ | **3.b** | 77 | 44 |




**3.g**: R = Ph
**3.h**: R = 2-Naph
**3.i**: R = 3,5-$^t$Bu$_2$-Ph




**3.v**: R = Ph
**3.x**: R = $^t$Bu




**3.j**: R = Ph
**3.k**: R = 1-Naph
**3.l**: R = 2-Naph
**3.m**: R = 3,5-$^t$Bu$_2$-Ph

[a] The reactions were performed in $CH_2Cl_2$ at 0 °C with 10 mol% of the catalyst, 1.0 eq. of enecarbamate (**1.37**) and 1.2 eq. of ethyl glyoxylate and subjected to acidic hydrolysis after 1 h, unless otherwise stated;
[b] The absolute configuration is *R*, except for entries 10-12 and 20;
[c] 30 mol% of catalyst was used;
[d] The reaction was performed at -20 °C;
[e] The reaction was performed at -78 °C.

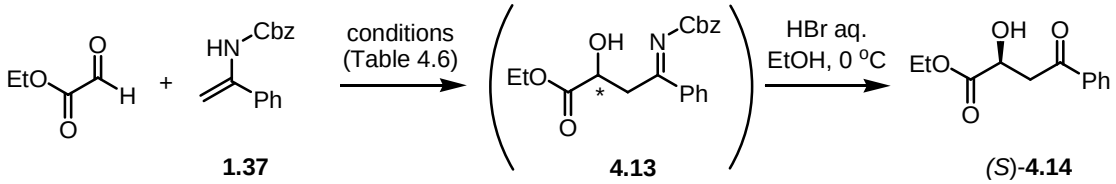
The reaction proceeded smoothly in all cases to afford, after acidic hydrolysis, the expected *β*-hydroxy ketone (**4.14**) in moderate to excellent yields (44% to quantitative). The source of copper(II) proved to be an important parameter for obtaining high yields and $Cu(OTf)_2$ systematically afforded the best results (entries 1 to 19 *versus* entries 20 to 23, Table 4.5, respectively). Unfortunately, only moderate enantiomeric excesses (up to 73%) were obtained, regardless of the chiral ligand used. In the diamine ligand series (entries 1 to 9 and 17 to 19, Table 4.5), the use of sterically more demanding ligands resulted in marginal improvements in the enantioselectivity but it had occasionally a serious detrimental effect on the reaction yield (*e.g.*, entry 6 (a catalyst prepared with a *tert*-butyl type ligand afforded the product in 58% yield and 57% *ee*) *versus* entry 7 (with a phenyl based ligand, the

product was obtained in 96% yield and 46% *ee*), Table 4.5). In this series of ligands, the best result (quantitative yield and 62% *ee*) was obtained with the bulky cyclohexyl-derived diamine ligand (**3.i**) (entry 19, Table 4.5). Interestingly, in the diimine ligand series (entries 13 to 16, Table 4.5), a somewhat opposite trend to that observed with the diamine ligands was noticed. The yields were, to some extent independent of the steric bulkiness of the ligand and less sterically demanding ligands afforded considerably higher enantiomeric excesses (*e.g.*, entry 16 (where a catalyst containing a ligand with *tert*-butyl moieties afforded the expected product in 68% yield but only 17% *ee*) *versus* entry 13 (where a catalyst with phenyl groups delivered the product in 65% yield and 70% *ee*), Table 4.5). Notably, the highest enantiomeric excess (73%) was obtained with a catalyst complex prepared from $Cu(OTf)_2$ and the widely used *tert*-butyl-Box ligand (**3.x**) (entry 12, Table 4.5). Attempts to increase the enantioselectivity by performing the reaction at lower temperatures resulted in only small improvements (*e.g.*, entry 1 (55% *ee* at 0 °C) *versus* entry 3 (58% *ee* at -20 °C), Table 4.5).

### 4.1.2.2.3 - Use of Copper(I)-Based Catalysts

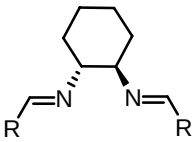
The use of copper(I) salts were then tested. The results are shown in Table 4.6.

**Table 4.6** Reaction of enecarbamate (**1.37**) with ethyl glyoxylate using Cu(I)-based catalysts.




**1.37** **4.13** (*S*)-**4.14**

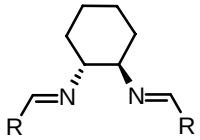
| Entry[a] | L.A. | Chiral Ligand | Yield (%) | *ee* (%)[b] |
|---|---|---|---|---|
| 1[b] | $CuClO_4 \cdot 4CH_3CN$ | **1.a** | 90 | 35 |
| 2 | | **3.j** | 94 | 93 |
| 3 | | **3.k** | 92 | 73 |
| 4 | | **3.l** | 52 | 68 |
| 5[c] | | **3.j** | 48 | 91 |
| 6[d] | | **3.j** | 97 | 93 |
| 7[e] | | **3.j** | quant. | 94 |
| 8[e] | | **3.n** | 97 | 81 |
| 9[e] | | **3.p** | quant. | 86 |




**3.j**: R = Ph
**3.k**: R = 1-Naph
**3.l**: R = 2-Naph
**3.n**: R = *o*-Tol
**3.p**: R = *m*-Tol

**Table 4.6** (*cont.*)

| Entry[a] | L.A. | Chiral Ligand | Yield (%) | *ee* (%)[b] |
|---|---|---|---|---|
| 10[e] | $CuClO_4 \cdot 4CH_3CN$ | **3.o** | 98 | 95 |
| 11[e,f] | | **3.o** | 20 | 17 |
| 12[e,g] | | **3.o** | traces | nd |
| 13[e] | | **3.q** | 87 | 94 |
| 14[e] | | **3.r** | 93 | 94 |
| 15[e] | | **3.s** | 97 | 96 |
| 16[e] | | **3.t** | 93 | 97 |
| 17[e] | | **3.u** | 93 | 97 |
| 18 | $CuSbF_6$ | **3.j** | 77 | 44 |
| 19 | $CuPF_6 \cdot 4CH_3CN$ | **3.j** | 94 | 82 |
| 20 | $CuOTf \cdot \frac{1}{2}C_6H_5CH_3$ | **3.j** | 66 | 78 |




**3.o**: R = *p*-Tol
**3.q**: R = *p*-EtPh
**3.r**: R = *p*-$^{i}$PrPh
**3.s**: R = *p*-FPh
**3.t**: R = *p*-ClPh
**3.u**: R = *p*-BrPh

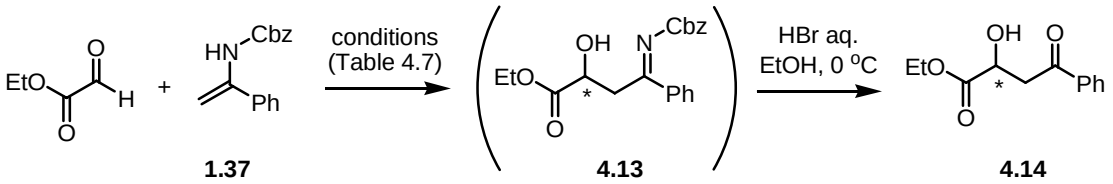
[a] The reactions were performed in $CH_2Cl_2$ at 0 °C with 10 mol% of the catalyst, 1.0 eq. of enecarbamate (**1.37**) and 1.2 eq. of ethyl glyoxylate and subjected to acidic hydrolysis after 1 h, unless otherwise stated;
[b] The absolute configuration of the product is (*S*), except for entry 1 (*R*);
[c] The reaction was performed at -78 °C;
[d] 1.5 eq. of ethyl glyoxylate was used;
[e] 2.0 eq. ethyl glyoxylate was used;
[f] Toluene was used as the solvent;
[g] Acetonitrile was used as the solvent.

The copper(I)-diamine and copper(I)-diimine catalysts are equally efficient at promoting the addition reaction of enecarbamate (**1.37**) to ethyl glyoxylate, with the expected *β*-hydroxy ketone (**4.14**) being obtained in good to excellent yields after acidic hydrolysis (66% to quantitative) (Table 4.6). The source of copper(I) was important to the reaction yields, and $CuClO_4 \cdot 4CH_3CN$ afforded the best results (*e.g.*, entry 2 ($CuClO_4 \cdot 4CH_3CN$, 94%) *versus* entries 18 & 20 ($CuSbF_6$, 77% and $CuOTf \cdot \frac{1}{2}C_6H_5CH_3$, 66%, respectively), Table 4.6). Furthermore, when diimine ligands were used, the *β*-hydroxy ketone (**4.14**) was formed with high to excellent enantiomeric excesses. The highest enantiomeric excess was obtained with a catalyst derived from $CuClO_4 \cdot 4CH_3CN$ and the *para*-halogenated-phenyl diimine ligands (**3.t**) and (**3.u**) (97% *ee*) (entries 16 & 17, respectively, Table 4.6). When the complex obtained from $CuClO_4 \cdot 4CH_3CN$ and diimine ligand (**3.j**) was used as the catalyst and the reaction was performed at -78 °C, the yield decreased markedly to 48%, although the expected *β*-hydroxy ketone (**4.14**) was still formed with 91 % enantiomeric excess (entry 5, Table 4.6).

### 4.1.2.2.4 - Use of Nickel(II)-Based Catalysts

Finally, nickel(II) was briefly investigated (Table 4.7).

**Table 4.7** Reaction of enecarbamate (**1.37**) with ethyl glyoxylate using Ni(II)-based catalysts.




**1.37** **4.13** **4.14**

| Entry[a] | L.A. | Chiral Ligand[b] | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | $Ni(OTf)_2$ | - | 58 | |
| 2 | | **3.d** | 87 | 56 |
| 3 | | **3.u** | 71 | 5 |
| 4 | | **3.x** | 84 | 86 |

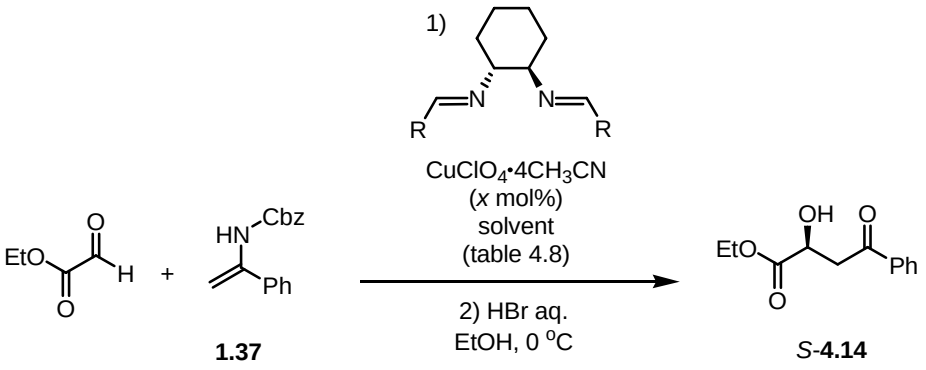
[a] The reactions were performed in $CH_2Cl_2$ at 0 °C with 10 mol% of the catalyst, 1.0 eq. of enecarbamate (**x.1**) and 1.2 eq. of ethyl glyoxylate and subjected to acidic hydrolysis after 1 h;
[b] "-" stands for "not used".

The expected *β*-hydroxy ketone (**4.14**) was produced in moderate to good yields (58% to 84%). However, with the exception of the widely used catalyst derived from $Ni(OTf)_2$ and the *tert*-butyl Box ligand (**3.x**), which afforded the product with good enantiomeric excess (86% *ee*) (entry 4, Table 4.7), the enantioselectivities obtained were only modest. On the other hand, a novel nickel(II)-based catalyst derived from $Ni(OTf)_2$ and the diamine ligand (**3.d**) was unveiled. Remarkably, this new catalyst promoted the formation of ketone (**4.14**) in a more enantioselective manner than the corresponding copper(II)-based catalyst (entry 2, Table 4.7 (nickel(II), 56% *ee*) *versus* entry 7, Table 4.5, (copper(II), 46% *ee*)). Some applications of this new catalyst will be demonstrated later (*vide infra*, Section 4.2.1.2.2).

### 4.1.2.2.5 - Effect of the Solvent and the Catalyst Loading

Having established that under the conditions studied the best catalytic system for the addition reaction is derived from $CuClO_4 \cdot 4CH_3CN$ and the diimine-type ligands (**3.t**) and (**3.u**), a brief evaluation of other variables that could affect the enantioselectivity of the process was performed. Accordingly, the solvent and the catalyst loading were investigated. The results are presented in Table 4.8.

**Table 4.8** Effect of the solvent and catalyst loading on the enantioselectivity of the reaction.




| Entry[a] | Solvent | Ligand | Catalyst Loading (*x* mol%) | Yield (%) | *ee* (%) |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | **3.o** | 10 | 98 | 95 |
| 2 | PhMe | **3.o** | 10 | 20 | 17 |
| 3 | $CH_3CN$ | **3.o** | 10 | traces | nd |
| 4[b] | $CH_2Cl_2$ | **3.u** | 10 | 93 | 97 |
| 5[b] | $CH_2Cl_2$ | **3.u** | 5 | 94 | 96 |
| 6[b] | $CH_2Cl_2$ | **3.u** | 2 | 96 | 95 |
| 7[b] | $CH_2Cl_2$ | **3.u** | 1 | 90 | 94 |

[a] The reactions were performed in the specified solvent at 0 °C with *x* mol% of the catalyst, 1.0 eq. of enecarbamate (**1.37**) and 2.0 eq. of ethyl glyoxylate and subjected to acidic hydrolysis after 1 h, unless otherwise stated

[b] 1.2 eq. of ethyl glyoxylate was used.

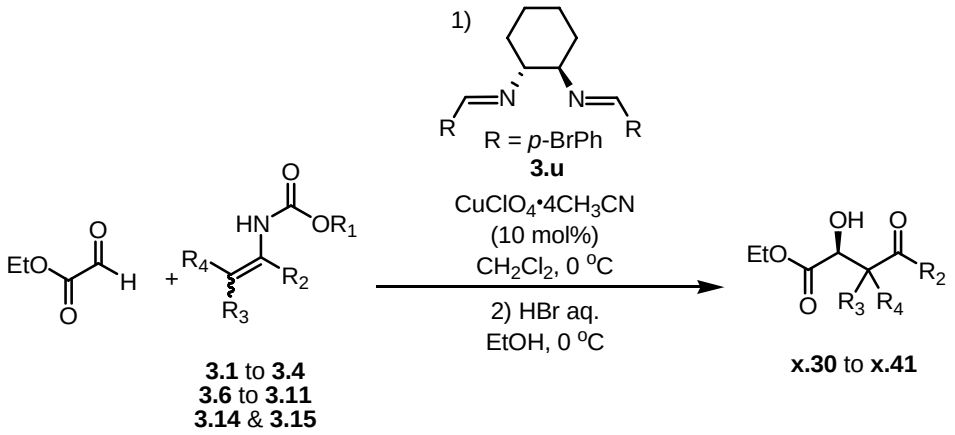
In toluene and acetonitrile, the catalytic activity of the resultant complexes decreased significantly and the *β*-hydroxy ketone (**4.14**) was formed only in low yields (up to 20%) (entries 2 & 3, Table 4.8,). With a set of optimal conditions determined concerning the metal source, ligand, and the solvent, the catalyst loading was minimized (entries 4 to 7, Table 4.8). As shown, even when only 1.0 mol% of the

catalyst was used, the *β*-hydroxy ketone (**4.14**) was still formed in high yield (90%) and with only a slightly reduced enantiomeric excess (94%) (entry 7, Table 4.8).

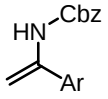
### 4.1.2.2.6 - Extension to Other Enecarbamates

Having determined the optimal reaction conditions to perform the addition of the prototype enecarbamate (**1.37**) to ethyl glyoxylate in an enantioselective manner, this process was then extended to other enecarbamates (Table 4.9).

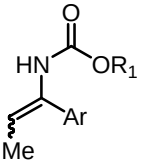
**Table 4.9** Reaction of various enecarbamates with ethyl glyoxylate.




| Entry[a] | Enecarbamate | Product | Yield (%) | *Syn*:*Anti* ratio[b] | *ee* (%)[b,c] |
|---|---|---|---|---|---|
| 1 | **3.1** | **4.17** | 94 | - | 93 |
| 2 | **3.2** | **4.18** | 97 | - | 97 |
| 3 | **3.3** | **4.19** | quant | - | 96 |
| 4 | **3.4** | **4.20** | 91 | - | 96 |
| 5 | *E*-**3.6** | *anti*-**4.21** | 83 | 1:99 | 98 |
| 6[d] | *E*-**3.6**[e] | *anti*-**4.21** | 93 | 1:99 | 97 |
| 7[d] | *E*-**3.6**[f] | *anti*-**4.21** | 95 | 1:99 | 98 |
| 8 | *Z*-**3.6** | *syn*-**4.21** | 82 | 98:2 | 98 |
| 9 | *Z*-**3.6**[e] | *syn*-**4.21** | 93 | 98:2 | 98 |
| 10 | *Z*-**3.6**[f] | *syn*-**4.21** | 96 | 98:2 | 98 |
| 11 | *E*-**3.7** | *anti*-**4.22** | 96 | 2:98 | 98 |
| 12 | *Z*-**3.7** | *syn*-**4.22** | 97 | 98:2 | 98 |



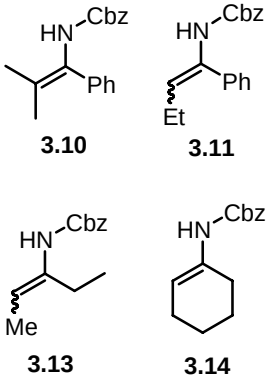

**3.1**: Ar = *p*-OMePh
**3.2**: Ar = *p*-ClPh
**3.3**: Ar = *p*-MePh
**3.4**: Ar = 2-Naph




**3.6**: $R_1$ = Bn, Ar = Ph
**3.7**: $R_1$ = Bn, Ar = *p*-OMePh
**3.8**: $R_1$ = Bn, Ar = *p*-ClPh
**3.9**: $R_1$ = Et, Ar = *p*-OMePh

**Table 4.9** *(cont.)*

| Entry[a] | Enecarbamate | Product | Yield (%) | *Syn*/*Anti* ratio[b] | *ee* (%)[b,c] |
|---|---|---|---|---|---|
| 13 | *E*-**3.8** | *anti*-**4.23** | 85 | 2:98 | 98 |
| 14 | *Z*-**3.8** | *syn*-**4.23** | 79 | 99:1 | 98 |
| 15 | *E*-**3.9** | *anti*-**4.24** | 82 | 3:97 | 96 |
| 16 | *Z*-**3.9** | *syn*-**4.24** | 96 | 99:1 | 98 |
| 17[g] | **3.10** | **4.25** | 22 | - | 84 |
| 18 | *E*-**3.11**[h] | *anti*-**4.26** | 58 | 1:99 | 98 |
| 19 | *Z*-**3.11** | *syn*-**4.26** | 92 | 99:1 | 98 |
| 20 | *E*-**3.13** | *anti*-**4.27** | 83 | 3:97[i] | 97 |
| 21[d] | *Z*-**3.13** | *syn*-**4.27** | 89 | 92:8[i] | 98 |
| 22[d] | **3.14** | *anti*-**4.28** | 85 | 16:84[i] | 94 |




**3.10** **3.11** **3.13** **3.14**

[a] The reactions were performed in $CH_2Cl_2$ at 0 °C with 10 mol% of the catalyst, 1.0 eq. of enecarbamate and 1.2 eq. of ethyl glyoxylate and subjected to acidic hydrolysis after 1 h, unless otherwise stated;
[b] Determined by HPLC;
[c] For entries 5-22 it corresponds to the enantiomeric excess of the major diastereomer.
[d] The reaction performed at -20 °C;
[e] 1 mol% of the catalyst was used and the reaction was quenched after approx. 36 h;
[f] 0.1 mol% of the catalyst was used and the reaction was quenched after approx. 46 h;
[g] The reaction was performed at rt and subjected to acidic hydrolysis after 28 h.
[h] 2.0 eq. of ethyl glyoxylate were used;
[i] Determined by NMR analysis.

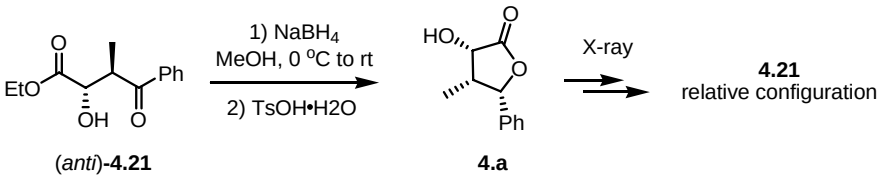
The enecarbamates (**3.1**) to (**3.4**) reacted with ethyl glyoxylate to afford the corresponding *β*-hydroxy ketones (**4.17**) to (**4.20**) in excellent yields (>91%) and with high enantiomeric excess (up to 97%) (entries 1 to 4, Table 4.9). When *α*-methyl-substituted enecarbamates (**3.6**) to (**3.9**) were used, the parent *α*-methyl-*β*-hydroxy benzophenones (**4.21**) to (**4.24**) were obtained in good yields (79% to 97%) (entries 5 to 16, Table 4.9). Furthermore, these reactions proceeded with very high diastereo- and enantioselectivities: the *syn*:*anti* ratios of the two diastereomers was always higher than 3:97 and 98:2, respectively, and the major diastereomer was formed with >95% enantiomeric excess. Notably, *E*-enecarbamates afforded products with the *anti*

configuration whereas *Z*-enecarbamates delivered the *syn*-adducts.[4.4] Decreasing the catalyst loading afforded slightly better yields, although lower temperature and prolonged reaction times were occasionally necessary. When 0.1 mol% of the catalyst was used and the reaction performed with *E*-(**3.6**) at -20 °C over approximately 46 h, *anti*-(**4.21**) was obtained in 95% yield, compared to 83% yield when using the standard conditions (entry 5 *vs.* entry 7, Table 4.9). The reaction could also be extended to more sterically demanding substrates. The *α,α'*-dimethyl enecarbamate (**3.10**) afforded the parent diketone (**4.25**) in good enantiomeric excess (84%) but in poor yield (22%) (entry 17, Table 4.9). On the other hand, the *α*-ethyl-substituted enecarbamates (**3.11**) delivered the corresponding *α*-ethyl-*β*-hydroxy benzophenone (**4.26**) with high diastereo- and enantioselectivities (entries 18 & 19, Table 4.9). The same trend regarding the high yields and good diastereo- and enantioselectivities of the *β*-hydroxy ketones products was observed for the aliphatic enecarbamates (**3.13**). On the other hand, the cyclohexanone-derived enecarbamate (**3.14**) reacted somewhat more sluggishly, affording the expected product (**4.28**) with a lower diastereoselectivity (*syn*:*anti*, 16:84) (entry 22, Table 4.9).

## 4.1.2.3 - Mechanistic Considerations

The catalyzed addition of enecarbamates to ethyl glyoxylate can be envisioned to take place either through an open, extended transition state or a closed, cyclic 6-membered transition state (Scheme 4.4 and Scheme 4.5, respectively).[4.5]

[4.4] The relative configuration of the *α*-methyl-*β*-hydroxy diketone (**4.21**) was determined by analysis of the X-ray crystal structure of the corresponding lactone (**4.a**), which was prepared from the former *via* $NaBH_4$ reduction and subsequent acid catalyzed cyclization (one pot) (Scheme 4.A).

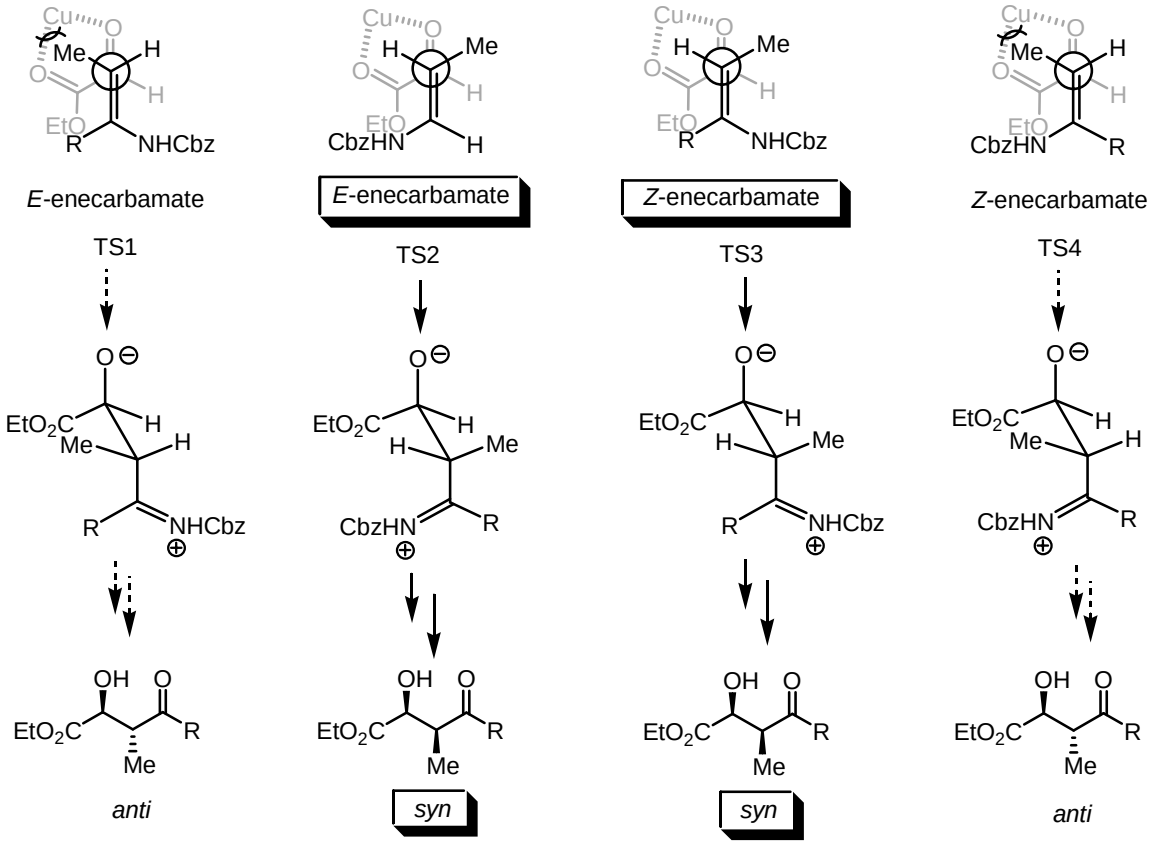



**Scheme 4.A** Determination of the relative configuration of *α*-methyl-*β*-hydroxy diketone (**4.21**).

The relative configuration of similar products was determined by analogy of the respective $^1$H-NMR spectra to that of *anti*-(**4.21**).

[4.5] Diastereoselectivities in additions of *π*-based nucleophiles (*e.g.*, silyl enol ethers, allylic organometallics, etc.) to aldehydes or ketones have been discussed extensively using open or cyclic transition state models. For aldol reactions, see: (a) Mahrwald, R. *Chem Rev.* **1999**, *99*, 1095. For allylations, see: (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. For effects of the olefin

In open, extended transition states the conformational freedom of the reactants complicates a detailed analysis of the reaction; thus it is not straight forward to predict which arrangement of the reactants (*e.g.*, *synclinal versus anticlinal*) is favored. A tentative analysis, based on an intuitively more likely *anticlinal* disposition between the *S-cis* conformation of the ethyl glyoxylate and the enecarbamate is shown in Scheme 4.4. *E*-enecarbamates are used in transition states TS1 and TS2 whereas *Z*-enecarbamates are used in TS3 and TS4. The steric interaction between the methyl group at the *α* position of the enecarbamate and the copper complex is expected to be larger in TS1 and TS4. Thus, TS2 and TS3 are predicted to be favored.



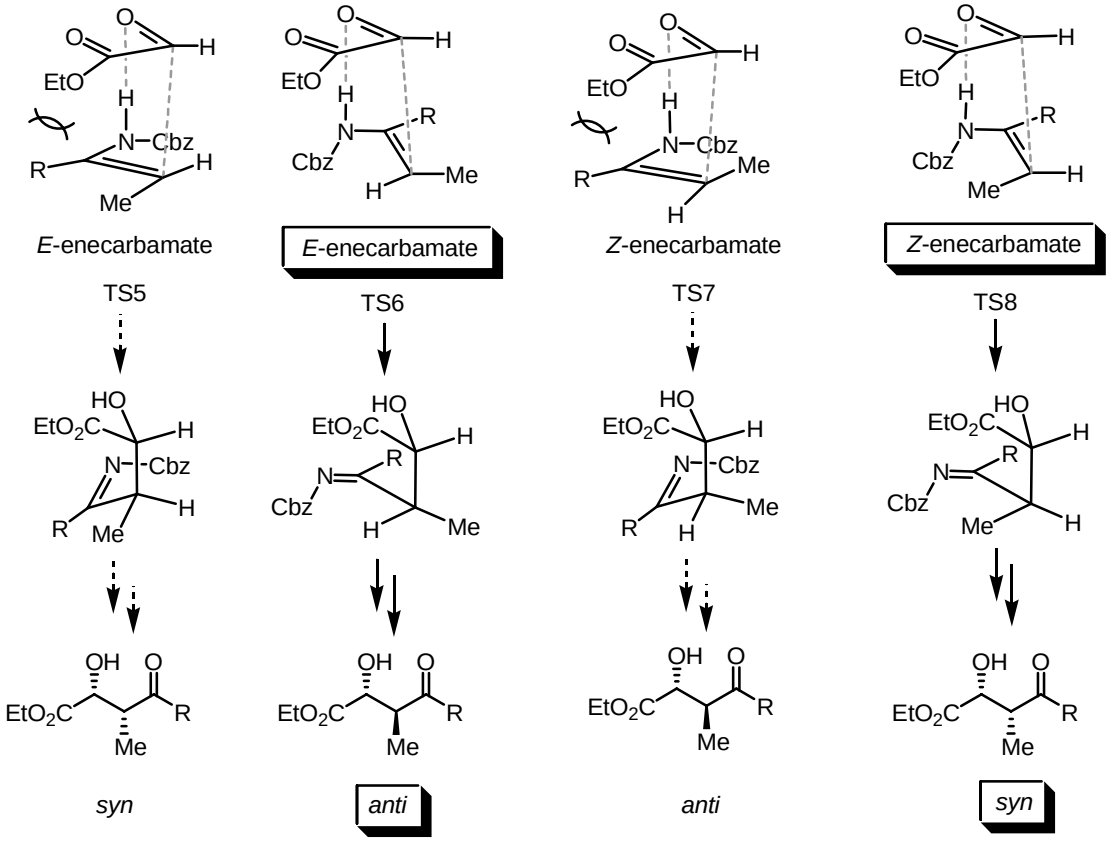

**Scheme 4.4** Models for hypothetical open, extended transition states.

Therefore, based on this type of transition state, both *E*- and *Z*- enecarbamates would stereoconvergently afford the *syn*-product, which contradicts the observed diastereoselectivity. Furthermore, no simultaneous proton transfer can occur in such

geometry on the diastereoselectivity, see: (c) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. J. Org. Chem. 1994, 59, 7889. (d) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.

open, extended transition states and hence formation of a high energy zwitterionic species would result for this process, making it unlikely.

On the other hand, in a closed, cyclic 6-membered transition state, the proton transfer from the nitrogen to the oxygen of ethyl glyoxylate is expected to be an easy process since, as a consequence of the compact arrangement between the reactants, these two centers are close together. This proton transfer can occur more or less concertedly with the development of the new carbon-carbon bond thus avoiding, as far as possible, the formation of an energetically disfavored charged intermediate. Possible closed, cyclic 6-membered transition states, corresponding to such aza-ene type mechanism, are shown in (Scheme 4.5).[4.6,4.7]



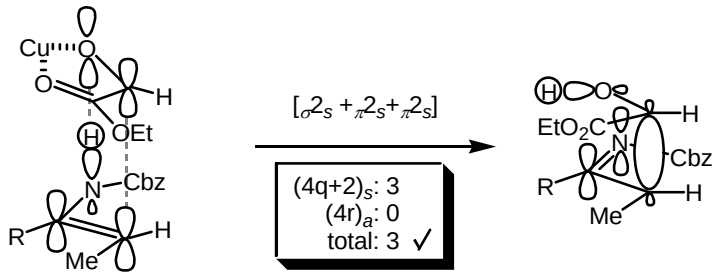

**Scheme 4.5** Models for closed, cyclic 6-membered transition states.

[4.6] For a review of aza-ene reactions, see: Borzilleri, R. M.; Weinreb, S. M. *Synthesis* **1995**, 347.

[4.7] A concerted aza-ene-type mechanism in Michael addition involving a chiral enamine has been previously proposed, see: (a) Ambroise, L.; Desmaële, D.; Mahuteau, J.; d'Angelo, J. *Tetrahedron Lett.* **1994**, *35*, 9705. (b) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.

*E*-enecarbamates are used in transition states TS5 and TS6 whereas *Z*-enecarbamates are used in TS7 and TS8. TS5 and TS7 are expected to be disfavored with respect to TS6 and TS8 due to an unfavorable 1,3-diaxial type interaction between the R group of the enecarbamate and the ethyl component of ethyl glyoxylate. This prediction is in agreement with the simple diastereoselection observed: *Z*-enecarbamates stereoselectively afford 1,2-*syn* products whereas *E*-enecarbamates deliver 1,2-*anti* adducts.

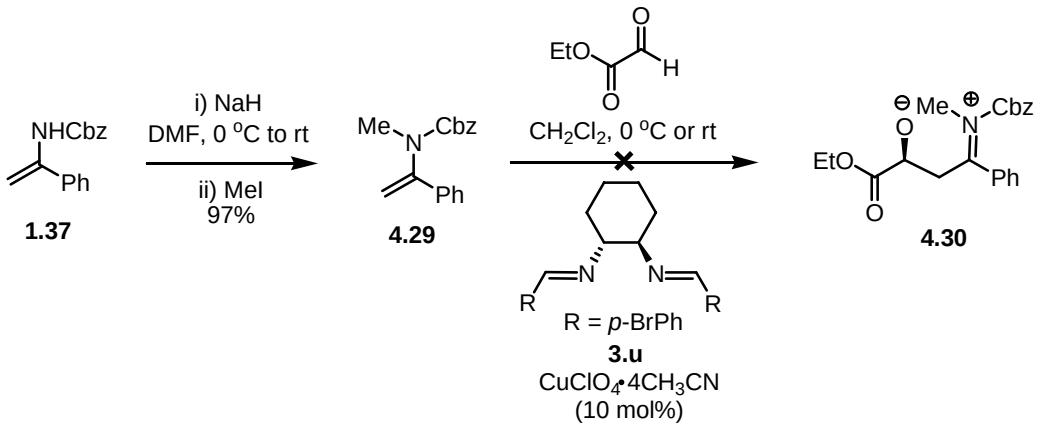
Such aza-ene type mechanism is in agreement with the Woodward-Hoffmann rules for pericyclic reactions,[4.8] illustrated as a 6-electron, all-suprafacial [$_\sigma 2+_\pi 2+_\pi 2$] process in Scheme 4.6. In order to allow the $\sigma$-overlap to develop properly head on and the $\pi$-overlap sideways on, the transition state for this atom-transfer reaction is proposed to have an envelope-type conformation.




**Scheme 4.6** Analysis of the proposed aza-ene type mechanism for the catalyzed addition reaction of enecarbamates to ethyl glyoxylate according to the Woodward-Hoffmann rules for pericyclic reactions.

To obtain more information about the reaction mechanism, the role of the proton at enecarbamate nitrogen was investigated. For this purpose the tertiary enecarbamate (**4.29**) was prepared and it was subsequently treated with ethyl glyoxylate in the presence of 10 mol% of $CuClO_4 \cdot 4CH_3CN$/diimine (**3.u**) (Scheme 4.7). That the reaction did not proceed, even at room temperature, to afford zwitterionic (**4.30**) shows that a transferable proton at the enecarbamate nitrogen is a necessary condition for this process, a result that further supports an aza-ene type of mechanism.

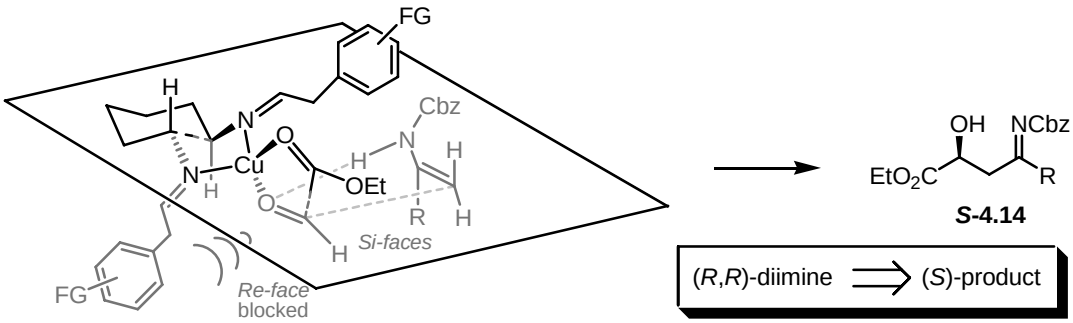
[4.8] (a) R. B. Woodward and R. Hoffmann in "The Conservation of Orbital Symmetry" **1970**, Verlag Chemie, Academidc Press, New York (b) Fleming, I. in "Pericyclic Reactions" **1999**, *67*, Oxford Science Publications, Oxford Chemistry Primers.




**Scheme 4.7** (Attempted) reaction of tertiary enecarbamate (**4.29**) with ethyl glyoxylate.

To gain an insight into the origin of the high stereoselectivity, we tried to gather information about the structure of the chiral copper(I) catalyst. However, all attempts to isolate it were unsuccessful.

Nonetheless, a putative working model that explains the observed diastereo- and enantioselectivity for such aza-ene type reaction catalyzed by the [Cu(I)-(*R*,*R*)-diimine (**3.u**))]·$ClO_4$ complex is shown in Scheme 4.8. The key features of this model are that it assumes a four-coordinate (eventually distorted) tetrahedral geometry at the copper(I) metal center and a two point catalyst-enophile binding. Therefore, the imine nitrogens of the ligand and the ethyl glyoxylate oxygens are held in (approximately) orthogonal planes whereas the ethyl glyoxylate is "locked" in the *S*-*cis* conformation. On the other hand, the two imine nitrogens of the chiral ligand are held in a *trans* arrangement by the cyclohexane ring group. The likely consequence of these geometric constrains, is that one of the "arms" of the chiral $C_2$ symmetric ligand effectively shields the *Re*-face of the ethyl glyoxylate hence leaving the *Si*-face available for approach by the *Si*-face of the enecarbamate. This model correctly correlates the chirality of the (*R*,*R*)-diimine ligand to the observed stereochemistry of the adduct (*S*)-(**4.14**).




**Scheme 4.8** Working model to account for the observed absolute stereochemistry in the addition reaction of enecarbamates to ethyl glyoxylate catalyzed by Cu(I)-$C_2$ symmetric diamine ligand

## 4.1.2.5 - Diastereoselective Reductions of Cbz-Protected *β*-Hydroxy Imines to Cbz-Protected *β*-Hydroxy Amines

Thus far, the primary product of the reaction of enecarbamates with ethyl glyoxylate, a protected *β*-hydroxy imine, was hydrolyzed to afford the corresponding *β*-hydroxy ketone. To further demonstrate the utility of enecarbamates as carbon nucleophiles, the (stereoselective) reduction of these *β*-hydroxy imine intermediates was investigated. If successful, this would allow the access to 1,3-hydroxy carbamates which could then be converted into the parent 1,3-amino alcohols. The latter are important compounds in organic chemistry, not only because they are useful synthetic intermediates but also important ligands for asymmetric catalysis.[4.9]

Whereas the stereoselective reduction of *β*-hydroxy ketones is well-known,[4.10] there are relatively few examples concerning the corresponding process for 1,3-iminoalcohols.[4.11] Furthermore, the reduction of a single *β*-hydroxy imine stereoisomer to either the *syn*- or *anti*-1,3 amino alcohol through the use of different reagents and reactions conditions is even rarer.[4.12]

---

[4.9] Hulst, R.; Heres, H.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 1373. (b) Li, X.; Yeung, C.-H.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 759. (c) Evans, P. A.; Holmes, A. B.; McGeary, R. P.; Nadin, A.; Russell, K.; O'Hanlon, P. J.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 123.

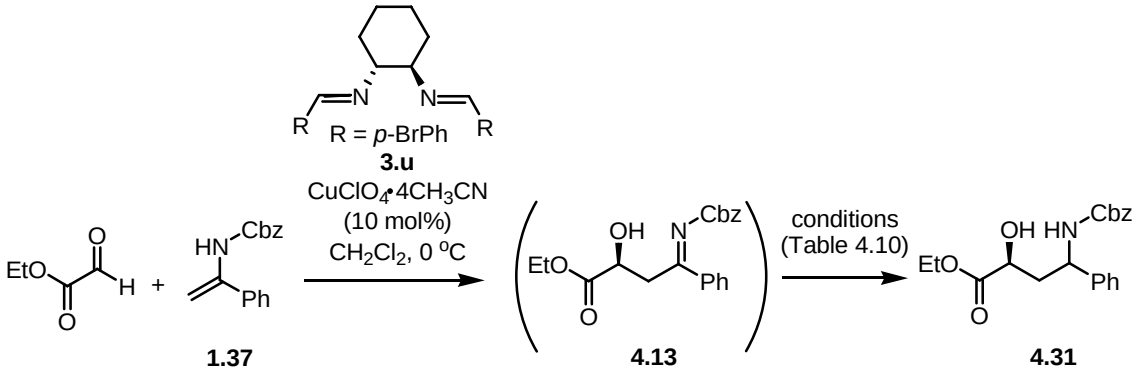
[4.10] For a review see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

[4.11] Some strategies to convert 1,3-hydroxy imines to either *syn*- or *anti*-1,3-amino alcohols by choosing an appropriate geometry of the imines or a suitable protecting group on the nitrogen have been reported, see: (a) Williams, D., R.; Osterhout, M., H. *J. Am. Chem. Soc.* **1992**, *114*, 8750. (b) Haddad, M.; Dorbais, J.; Larcheveque, M. *Tetrahedron Lett.* **1997**, *38*, 5981.

[4.12] To the best of the author's knowledge this has only been accomplished with *β*-hydroxy *N*-sulfinly imines, see: Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276.

Therefore, the goal for this reduction step was twofold: i) to accomplish the reduction diastereoselectively and ii) to identify conditions to selectively access both *syn*- and *anti*-1,3-hydroxy carbamates from a common precursor. Our efforts towards these ends are presented in Table 4.10.[4.13] We concentrated on some of the most commonly used reducing agents for the diastereoselective conversion of *β*-hydroxy ketones into the parent 1,3-diols.[4.10]

**Table 4.10** Preparation of *β*-hydroxy carbamate (**4.31**) *via* the reduction of the *β*-imino alcohol intermediate (**4.13**).




| Entry[a] | Reagent (eq.) | Additive (eq.)[b] | Solvent | T (°C) | t (h) | Yield (%)[c] | *syn*:*anti* ratio[d] |
|---|---|---|---|---|---|---|---|
| 1 | $Zn(BH_4)_2$ (2.0) | - | $Et_2O$ | 0 | 2 | traces | nd |
| 2 | $Zn(BH_4)_2$ (1.0) | - | $Et_2O$ | -78 | 1 | <65 | 71:29 |
| 3 | $Zn(BH_4)_2$ (2.0) | - | $Et_2O$ | -78 | 3 | <48 | 86:14 |
| 4 | $Zn(BH_4)_2$ (1.0) | - | $Et_2O$ | -78 | 3 | <66 | 78:22 |
| 5[e] | $Zn(BH_4)_2$ (1.0) | 4Å MS | $Et_2O$ | -78 | 3 | <75 | 78:22 |
| 6 | $Zn(BH_4)_2$ (1.0) | - | PhMe-$Et_2O$ (1:1) | -78 | 1 | <75 | 75:25 |
| 7 | $NaBH_4$ (2.0) | - | EtOH | 0 | ½ | <16 | 67:33 |
| 8 | $NaBH_4$ (2.0) | - | EtOH | -78 | 24 | 68 | 59:41 |

[4.13] Most of the results in this section should be credited to Ryosuke Matsubara.

**Table 4.10** (*cont.*)

| Entry[a] | Reagent (eq.) | Additive (eq.)[b] | Solvent | T (°C) | t (h) | Yield (%)[c] | *syn*:*anti* ratio[d] |
|---|---|---|---|---|---|---|---|
| 9 | $LiAlH(O^tBu)_3$ (3.0) | - | $Et_2O$ | 0 | 2 | 0 | - |
| 10 | $LiAlH(O^tBu)_3$ (5.0) | - | $Et_2O$ | -78 | 20 | traces | nd |
| 11 | $LiAlH(O^tBu)_3$ (5.0) | LiI (5.0) | $Et_2O$ | -78 | 20 | traces | nd |
| 12 | 9-BBN (3.0) | - | THF | -20 | 16½ | traces | nd |
| 13 | Catecholborane (5.0) | - | THF | -78 | 24 | traces | nd |
| 14 | K-Selectride (2.2) | - | THF | -20 | 1.2 | traces | nd |
| 15 | K-Selectride (2.2) | - | THF | -45 | 4 | 0 | - |
| 16 | K-Selectride (2.2) | - | THF | -78 | 4 | 0 | - |
| 17 | L-Selectride (2.2) | - | THF | -20 | 16½ | <59 | 22:78 |
| 18 | $NaBH_4$ (2.0) | $ZnCl_2$ (1.5) | MeOH | -78 | 5½ | traces | nd |
| 19 | $NaBH_4$ (2.2) | $Et_2B(OMe)$ (1.1) | THF-MeOH (4:1) | -78 | 3 | <60 | 94:6 |
| 20 | $NaBH_4$ (2.2) | $Et_2B(OMe)$ (1.1) | THF-MeOH (4:1) | -45 | 3 | <68 | 91:9 |
| 21 | $NaBH_4$ (2.2) | $Et_2B(OMe)$ (2.2) | THF-MeOH (4:1) | -78 | 5½ | 55 | 91:9 |
| 22 | $NaBH_4$ (2.2) | $Et_2B(OMe)$ (2.2) | THF-MeOH (4:1) | -45 | 5½ | 69 | 88:12 |
| 23 | $NaBH_4$ (2.2) | $Et_2B(OMe)$ (2.2) | THF-MeOH (3:2) | -78 | 2 | <37 | nd |
| 24 | $NaBH_4$ (3.0) | $Et_2B(OMe)$ (3.0) | THF-MeOH (4:1) | -78 | 2 | 65 | 94:6 |

[a] The 1st step of the reactions was performed in $CH_2Cl_2$ at 0 °C with 10 mol% of the catalyst, 1.0 eq. of enecarbamate (**x.1**) and 1.2 eq. of ethyl glyoxylate and the resulting crude *β*-imino alcohol (**4.13**) was subjected to the 2nd step (reduction) typically after 1 h;

[b] "-" stands for "not used";

[c] A small amount of unknown impurities was always present except in entries 15, 16 and 18;

[d] "nd" stands for "not determined";

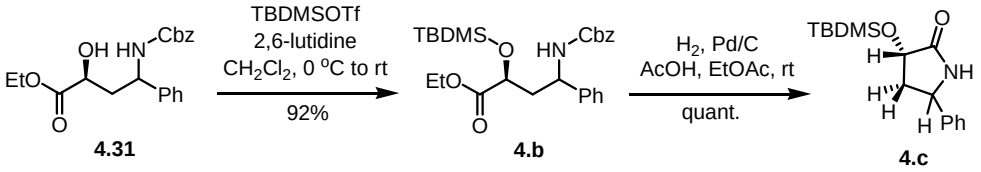
[e] An amount of 10 mg of 4Å MS *per* 0.1 mmol of substrate was used.

The use of $Zn(BH_4)_2$[4.14] was investigated under a variety of conditions (entries 1 to 6, Table 4.10). When the reaction was performed at 0 $^oC$, extensive decomposition of the starting 1,3 hydroxy imine (**4.13**) was observed (entry 1, Table 4.10). On the other hand, when the reduction was carried at -78 $^oC$ the expected 1,3-hydroxy carbamate (**4.31**) was obtained in moderate to good yields (approximately 50% to 75%) and good *syn*-selectivities (*syn*:*anti* ratio up to 86:14) (entries 2 to 6, Table 4.10).[4.15] $NaBH_4$ was able to deliver the 1,3-hydroxy carbamate (**4.31**) but it proved to be inferior to $Zn(BH_4)_2$, both with respect to the reaction yields (up to only 68%) (entry 8, Table 4.10) and the diastereoselectivity (67:33, *syn*:*anti* ratio,) (entry 7, Table 4.10). On the contrary, $LiAlH(OtBu)_3$, 9-BBN, catecholborane and K-Selectride afforded only traces or none of the desired product under the conditions investigated (entries 9 to 16, Table 4.10). Interestingly, when L-Selectride was used instead of K-Selectride, the expected 1,3-hydroxy carbamate (**4.31**) was produced in modest yield (approximately 60%) and with moderate *anti*-selectivity (*syn*:*anti* ratio, 22:78,) (entry 17). The best result regarding the diastereoselectivity of this process was obtained with the combination $NaBH_4$-$Et_2B(OMe)$[4.16] in a THF-MeOH mixture mainly at -78 $^oC$ (entries 19 to 24, Table 4.10). After some optimization the expected 1,3-hydroxy carbamate (**4.31**) could be obtained with very high *syn*-selectivities (*syn*:*anti* ratio up to 94:6) although only in modest yield (around 60%) (entry 24, Table 4.10).

The stereoselectivities observed in the above reduction are related with the ability of the several reducing agents to distinguish between the different conformations of the Cbz-protected *β*-hydroxy imine (**4.13**) in solution. In the cases where $Zn(BH_3)_2$ and $NaBH_4$-$Et_2B(OMe)$ were used, the imine (**4.13**) is likely to be present as a stable 6-

4.14 (a) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653. (b) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411.

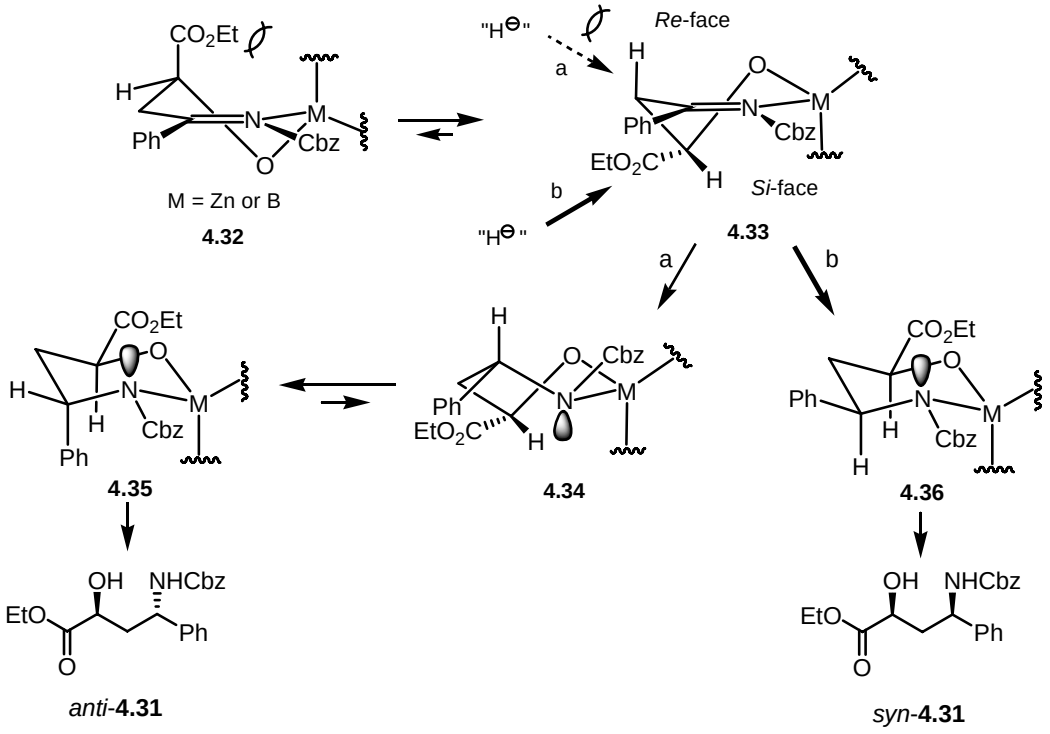
4.15 The relative configuration of the products (**4.31**) was determined by NOE experiments in the lactam (**4.c**) which was prepared from (**4.31**) *via* TBDMS protection of the alcohol functionality, followed by hydrogenolysis of the Cbz protecting group and *in situ* cyclization (Scheme 4.B).




**Scheme 4.B** Derivatization of (**4.31**) to determine the relative configuration.

4.16 (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233. (b) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

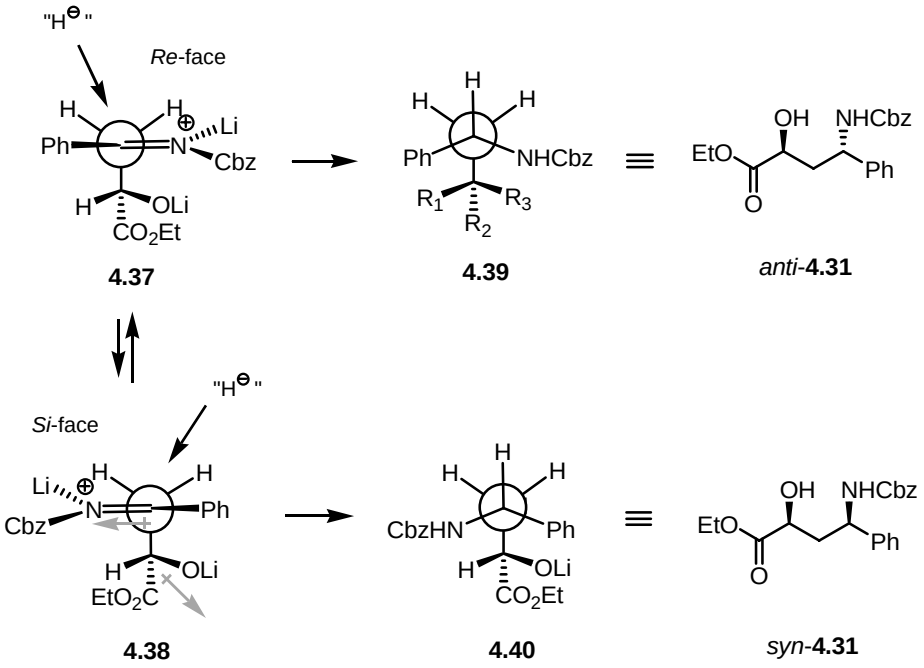
membered cyclic chelate.[4.14,4.16] Among the different conformers corresponding to such arrangement, the twisted-chair (**4.33**) is expected to be the most populated; the alternative twisted-chair conformer (**4.32**) is destabilized due to 1,3-axial type interactions between the ester group and the substituents on the metal (Zimmerman-Traxler-type analysis). The achievement of the high *syn*-1,3-asymmetric induction observed can then be explained by the preferential approach of the reducing agent from the *Si*-face of conformer(**4.33**). This bias partially results from the stereoelectronic effects that control such type of reactions: additions to iminium-type ions proceed in such a way that the lone pair on the nitrogen develops antiperiplanar with respect to the incoming nucleophile.[4.17] Thus, whereas hydride delivery to the *Re*-face of the iminium species (**4.33**) leads to the unfavorable twist-boat type intermediate (**4.34**), which affords the minor *anti*-(**4.31**) product, addition to the *Si* face proceeds through the more stable chair-type intermediate (**4.36**) hence delivering major *syn*-(**4.31**). In addition, it is likely that the axial H at the *α* position will also contribute in shielding the hydride approach from the *Re* face.




**Scheme 4.9** Proposed chelation-controlled mechanism leading to the *syn*-(**4.32**) as the major product.

[4.17] A. J. Kirby in "Stereoelectronic Effects" **1996**, *36*, Oxford Science Publications, Oxford Chemistry Primers.

On the other hand, the slight preference for the formation of the *anti*-product observed when bulky L-Selectide was used should be rationalized by considering an open-chain model for the addition.[4.18] Accordingly, the most stable conformer of the lithium-salt of the *β*-hydroxy imine (**4.13**) should be such that, in order to avoid Pitzer strain, all bonds are staggered. One can further assume, again for steric reasons, an *anticlinal* arrangement between the iminium group and the bulkiest substituent at the *β* position, presumably the ester. If so conformers (**4.37**) and (**4.38**), shown in Scheme 4.10, are likely to be almost equally populated, which would result in the formation of the diastereomeric products *anti*-(**4.31**) and *syn*-(**4.31**), respectively, in approximately equal amounts. The origin of the small difference in energy favoring (**4.37**) is perhaps the result of a preferred interaction between the iminium-phenyl and the H at the *β* position (Scheme 4.10).




**Scheme 4.10** Proposed open-chain mechanism leading to the *anti*-(**4.31**) as the major product.

[4.18] For open-chain models dealing with 1,3-asymmetric induction and applications, see: (a) Brienne, M-J.; Ouannès, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1968**, *3*, 1036. (b) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011 and 4019. (c) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537. (d) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *116*, 4322. (e) Bonini, C.; Esposito, V.; D'Auria, M.; Righi, G. *Tetrahedron* **1997**, *53*, 13419.

It should be noted that an argument favoring the conformer leading to the *syn*-configured (**4.31**) could equally have been put forward. In fact, on the ground of electrostatic factors, conformer (**4.38**) is expected to be favored over (**4.37**) as the interaction between the dipoles associated with the iminium bond and the net dipole from the $C_\beta$-OLi and $C_\beta$-$CO_2$Et is minimized in the former.

## 4.2 - Addition to *α,α'*-Diketones

Having developed a highly diastereo- and enantioselective catalyzed addition reaction of enecarbamates to ethyl glyoxylate, the possibility of extending this methodology to *α,α'*-diketones was next investigated.

### 4.2.1 - Use of Butane-2,3-dione as Substrate

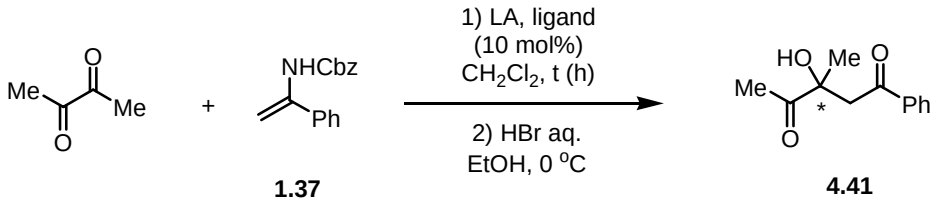
#### 4.2.1.1 - Catalyzed addition reaction of enecarbamates to Butane-2,3-dione

The initial studies were conducted with the $C_2$-symmetrical butane-2,3-dione and enecarbamate (**1.37**). As with ethyl glyoxylate, the crude reaction mixtures were subjected to acidic hydrolysis to give diketone products as these are easier to handle and analyze. The results obtained are shown in Table 4.11.

Identical reaction conditions to those that afforded the best results in the ethyl glyoxylate case (*i.e.*, reaction performed at 0 $^oC$ using a catalyst derived from $CuClO_4 \cdot 4CH_3CN$ and dimine (**3.u**) and quenching the reaction after 1 h) were initial tested. However, under these conditions, the addition reaction did not proceed (entry 1, Table 4.11). When a considerably longer reaction time was used the expected diketone (**4.41**) was isolated although in very low yield (5%) and modest enantiomeric excess (47% *ee*) (entry 2, Table 4.11). This marked difference in behavior between ethyl glyoxylate and butane-2,3-dione was ascribed to the less pronounced electrophilic character of the latter. Thus, while the weak Lewis acidic copper(I)-diimine (**3.u**) catalyst is able to promote the stereoselective addition of enecarbamates to ethyl glyoxylate, it seems that it can not provide enough activation in the diketone case. Therefore, somewhat harsher conditions were used, namely stronger Lewis acids and/or higher temperatures and/or longer reaction times. When $BF_3 \cdot OEt_2$ was used and the reaction was performed at room temperature over 9 h, the

expected diketone (**4.41**) was not formed, presumably due to extensive decomposition of the enecarbamate (**1.37**) under these conditions (entry 3, Table 4.11).

**Table 4.11** Reaction of enecarbamate (**1.37**) and butane-2,3-dione - I.




| Entry[a] | L.A. | Ligand | T (°C) | t (h) | Yield (%) | *ee* (%) |
|---|---|---|---|---|---|---|
| 1 | $CuClO_4 \cdot 4CH_3CN$ | **3.j** | 0 | 1 | 0 | - |
| 2 | $CuClO_4 \cdot 4CH_3CN$ | **3.i** | 0 | 9 | 5 | 47 |
| 3 | $BF_3 \cdot OEt_2$ | - | 0 to rt | 9 | 0 | - |
| 4 | $Cu(OTf)_2$ | **1.a** | 0 to rt | 9 | 58 | 30 |
| 5 | $Cu(OTf)_2$ | **3.d** | 0 to rt | 9 | 61 | 22 |
| 6[b] | $Cu(OTf)_2$ | **3.d** | 0 to rt | 15 | 68 | 2 |
| 7[c] | $Cu(OTf)_2$ | **3.d** | 0 to rt | 9 | 63 | 42 |

[a] The reactions were performed in $CH_2Cl_2$ at the stated temperature with 1.2 eq. of enecarbamate (**1.37**) being added to a solution of 10 mol% of the catalyst, and 1.0 eq. of butane-2,3-dione and subjected to acidic hydrolysis after the time stated, unless otherwise stated;

[b] An amount of 10 mg of 3Å MS *per* 0.1 mmol of substrate was added to the (preformed) catalyst solution;

[c] A solution of the catalyst was cannulated in three portions (1 h intervals) to an ice cold solution of the enecarbamate and the diketone.

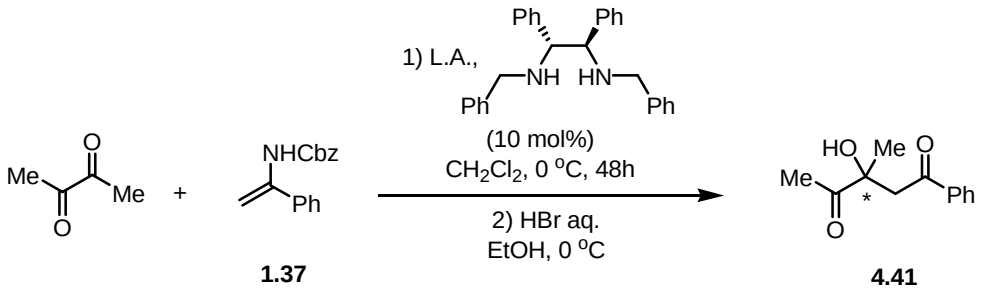
Better results were obtained when catalysts derived from $Cu(OTf)_2$ and diamine ligands were used and the reactions performed at room temperature over longer reaction times; with these conditions diketone (**4.41**) was isolated in moderate yields (58% to 68%) and with modest enantiomeric excess (up to 30%) (entries 4 to 6, Table 4.11). The use of bulkier diamine ligands had a (small) positive effect in the enantioselectivity of the reaction: diketone (**4.41**) was formed with 30% *ee* when the napthly-based (**1.a**) ligand was employed whereas the use of the corresponding phenyl-based (**3.d**) ligand delivered the product with 22% *ee* (entry 4 *vs.* entry 5, Table 4.11, respectively). The use of molecular sieves was detrimental both to the rate as well as on the enantioselectivity of the reaction (entry 6, Table 4.11). Notably, using an inverse addition procedure (where the catalyst solution was slowly added to a solution of the reactants) was advantageous for the reaction enantioselectivity: using these conditions, the diketone (**4.41**) was obtained with 42% *ee* (entry 7, Table 4.11).

## 4.2.1.2 - Enantioselective Catalyzed Addition Reaction of Enecarbamates to Butane-2,3-dione

### 4.2.1.2.1 - General Screening of Catalysts

Having determined that the catalyzed addition of enecarbamates to *α,α'*-diketones is feasible, the corresponding enantioselective version of this process was next investigated. The initial results concerning the effect of the metal centre are shown in Table 4.12.

**Table 4.12** Reaction of enecarbamate (**1.37**) and butane-2,3-dione - II.




**1.37** **4.41**

| Entry[a] | L.A. | Yield (%) | *ee* (%) |
|---|---|---|---|
| 1 | $Cu(OTf)_2$ | 72 | 71 |
| 2[b] | $Cu(OTf)_2$ | 85 | 74 |
| 3 | $CuOTf{\cdot}½PhH$ | 14 | 57 |
| 3 | $Ni(OTf)_2$ | 67 | 76 |
| 4 | $Zn(OTf)_2$ | 31 | 75 |
| 5 | $Co(OTf)_2$ | 5 | 45 |
| 6 | $Sc(OTf)_3$ | 0 | - |

[a] The reactions were performed in $CH_2Cl_2$ at 0 °C with 10 mol% of the catalyst (in a concentration of 7 mM),.1.0 eq. of enecarbamate (**1.37**) and 2.0 eq. of butane-2,3-dione and subjected to acidic hydrolysis after 48 h, unless otherwise stated;
[b] A solution of the catalyst was added over 6 h to a -20 °C solution of the reactants (inverse addition) and kept at this temperature for approx. 60 h, after which it was subjected to acidic hydrolysis.

When the reaction was performed in the presence of $Cu(OTf)_2$-diamine (**3.d**) (10 mol%) at 0 °C using two equivalents of butane-2,3-dione and quenched after 48 hours (acidic hydrolysis), the expected diketone (**4.41**) was formed in good yield (72%) and good enantiomeric excess (71%) (entry 1, Table 4.12). This result could be enhanced by performing the reaction at -20 °C and using an inverse addition protocol; with

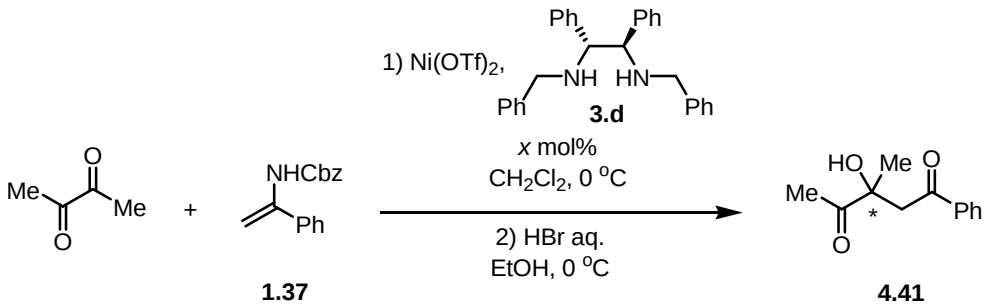
these conditions diketone (**4.41**) was isolated in 85% yield and 76% *ee* (entry 2, Table 4.12). In agreement with the preliminary screening, a comparison between catalysts derived from copper(II) and copper(I) triflates showed the former to be superior: the use of CuOTf·½PhH was detrimental, both with respect to the reaction yields (14%) and the enantioselectivity (57% *ee*) (entry 3, Table 4.12).We then investigated the use of other cationic transition metal triflates complexes of the same diamine (**3.d**) as catalysts for this reaction. The new nickel(II)-diamine (**3.d**) catalyst discovered during the ethyl glyoxylate studies (*vide supra*, section 4.1.2.2.4) proved to be as efficient as the corresponding copper(II) complex: whereas $Cu(OTf)_2$ afforded a slightly better yield than $Ni(OTf)_2$ (72% *versus* 67%, respectively), the obtained enantiomeric excess was slightly higher with the latter (76% *versus* 71%, respectively) (entry 1 *versus* entry 3, Table 4.12). $Zn(OTf)_2$ is was less efficient promoter of the addition reaction as the product diketone (**4.41**) was obtained in only 31% yield, although it does so with similar selectivity to $Cu(OTf)_2$ and $Ni(OTf)_2$: diketone (**4.41**) was formed with 74% *ee* (entry 4, Table 4.12). $Co(OTf)_2$ afforded diketone (**4.41**) only in very low yield (5%) and with low enantiomeric excess (45%) (entry 5, Table 4.12). Finally, $Sc(OTf)_3$ failed to catalyze the reaction under the conditions used (entry 6, Table 4.12).

### 4.2.1.2.2 - Use of the Nickel(II)-Diamine (3.d) Catalyst

Since $Ni(OTf)_2$ delivered the highest enantiomeric excess and because it is relatively under-studied as a Lewis acid with respect to its first row neighbours, this LA was chosen for further studies. Furthermore, the choice of nickel allowed us to focus on the use of the new $Ni(OTf)_2$-diamine (**3.d**) catalyst that was discovered previously (*vide supra*, section 4.1.2.2.4).[4.19] The effect of the reaction temperature, catalyst loading and concentration were investigated and the results are presented in Table 4.13.

[4.19] For representative examples of nickel(II) complexes as chiral L.A. in catalysis see: (a) Evans, D. A.; Downey, W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706. (b) Kanemasa, S.; Oderaotoshi, Y.; Wada, E.; *J. Am. Chem. Soc.* **1999**, *121*, 8675. (c) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (d) Suga, H.; Kakehi, A.; Mitsuda, M. *Chem. Lett.* **2002**, 900. (e) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240. (f) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431.

**Table 4.13** Reaction of enecarbamate (**1.37**) with butane-2,3-dione using the $Ni(OTf)_2$-diamine(**3.d**) catalyst.




| Entry[a] | *x* mol% | Catalyst (mM) | Solvent | Yield (%) | *ee* (%) |
|---|---|---|---|---|---|
| 1 | 10 | 7 | $CH_2Cl_2$ | 67 | 76 |
| 2[b] | 10 | 7 | $CH_2Cl_2$ | - | - |
| 3[c] | 10 | 7 | $CH_2Cl_2$ | 27 | 49 |
| 4[d] | 10 | 7 | $CH_2Cl_2$ | 94 | 84 |
| 5 | 15 | 7 | $CH_2Cl_2$ | 33 | 76 |
| 6 | 5 | 7 | $CH_2Cl_2$ | 15 | 79 |
| 7 | 6 | 3 | $CH_2Cl_2$ | 17 | 77 |
| 8 | 6 | 12 | $CH_2Cl_2$ | 20 | 69 |
| 9 | 10 | 8 | PhMe | 47 | 75 |
| 10 | 10 | 8 | PhMe:$CH_2Cl_2$ (4:1) | 46 | 80 |
| 11 | 10 | 8 | PhMe:$CH_2Cl_2$ (1:1) | 32 | 80 |
| 12 | 10 | 8 | $Et_2O$ | 26 | 70 |

[a] The reactions were performed in the stated solvent at 0 °C with the *x* mol% of catalyst, 1.0 eq. of enecarbamate (**1.37**) and 2.0 eq. of butane-2,3-dione and subjected to acidic hydrolysis after 48 h, unless otherwise mentioned;
[b] The reaction was performed at -30 °C; precipitate observed after approx. ½ h; the reaction was quenched after 72 h;
[c] The reaction was performed at 40 °C; precipitate observed after approx. 17 h; the reaction was quenched after 24 h;
[d] The reaction was quenched after 14 days.

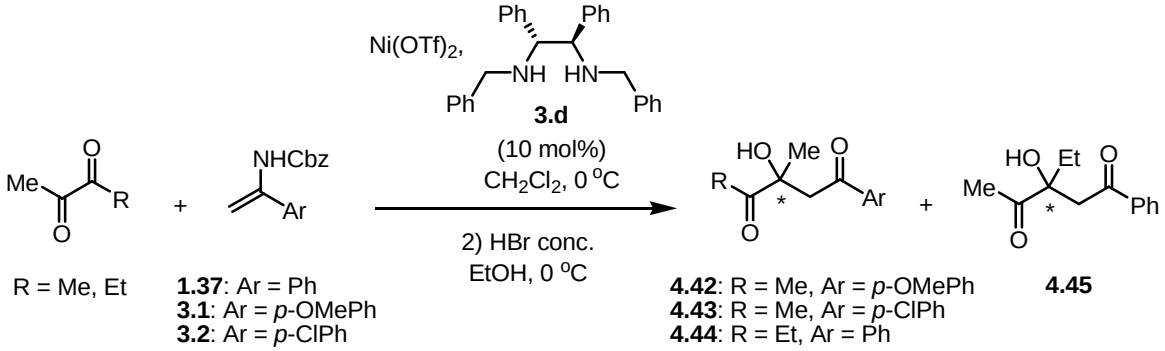
Attempts to improve the enantioselectivity by performing the reaction at a lower temperature (-30 °C) only led to disappointing results; under these conditions the reaction did not proceed at all, presumably because the catalyst is not stable at this temperature (entry 2, Table 4.13). No improvement resulted either by heating the reaction (40 °C) (entry 3, Table 4.13). When the reaction was allowed to proceed over 14 days (!), noticeable improvements, particularly in the reaction yield, were observed: the diketone (**4.41**) was isolated in 94% yield and 84% enantiomeric excess (entry 4, Table 4.13). This result has as important corollaries that i) the $Ni(OTf)_2$-

diamine (**3.d**) is a useful Lewis acid for the activation of α,α'-diketones in the enantioselective addition with enecarbamates and ii) the reaction is only limited by the turnover frequency and not catalyst inhibition or decomposition. An increase in the catalyst loading (from 10 mol% to 15 mol%) surprisingly lead to a considerable decrease in the reaction yield (67% to 33%), although the enantiomeric excess of diketone (**4.41**) was unaffected (76%) (entry 5 *versus* entry 1, respectively, Table 4.13). Reducing the catalyst loading (5 mol%) resulted in a pronounced reduction of the reaction yield (15%) whereas a minor improvement in the enantiomeric excess of the expected diketone (**4.41**) was observed (79%) (entry 6, Table 4.13). A simultaneous reduction in the loading and concentration of the catalyst (6 mol% and 3 mM, respectively) had a dramatic negative effect on the reaction yield (17%) while the enantiomeric excess improved marginally (77%) (entry 7, Table 4.13). Decreasing the catalyst loading while performing the reaction at a higher catalyst concentration (6 mol% and 12 mM, respectively) had a detrimental effect both on the enantioselectivity (69% *ee*) and the reaction yield (17%). Such marked variations of the reaction yield and enantioselectivity with the catalyst loading and concentration suggest a complex reaction mechanism, possibly due to aggregation phenomena in solution. The effect of solvent was also briefly investigated (entries 9 to 12, Table 4.13). Toluene proved to be inferior to $CH_2Cl_2$ regarding the reaction yield (47%), although diketone (**4.41**) was obtained with good enantiomeric excess (75% *ee*) (entry 9, Table 4.13). A mixture of toluene and $CH_2Cl_2$ (4:1) afforded diketone (**4.41**) with an improved enantiomeric excess (80%), but in reduced yield (46%) (entry 10, Table 4.13). Similar results were obtained with a mixture of toluene and $CH_2Cl_2$ (1:1) (entry 11, Table 4.13). Finally, when the reaction was performed in ether, diketone (**4.41**) was formed in low yield (26%) and with a decreased enantiomeric excess (70% *ee*) (entry 12, Table 4.13), possibly as a consequence of the coordinating properties of this solvent.

## 4.2.2 – Extension to Other Enecarbamates and *α,α'*-Diketones

The use of other *α,α'*-diketones and enecarbamates in this process was also briefly examined. The results are shown in Table 4.14.

**Table 4.14** Reaction of various enecarbamates with butane-2,3-dione and pentane-2,3-dione.




| Entry[a] | *α,α'*-diketone | Enecarbamate | Yield (%) | *ee* (%) |
|---|---|---|---|---|
| 1 | Butane-2,3-dione | **3.1** | 47 | 45 |
| 2[b] | | **3.1** | 59 | 65 |
| 3 | | **3.2** | 20 | 75 |
| 4[b] | | **3.2** | 90 | 82 |
| 5[c] | | **3.1** | 84 | 35 |
| 6[c] | | **3.2** | 44 | 38 |
| 7 | Pentane-2,3-dione | **1.37** | 17:2[d] | 84:63[d] |
| 8[b] | | **1.37** | 87:12[d] | 83:41[d] |

[a] The reactions were performed in $CH_2Cl_2$ at 0 °C with 10 mol% of the catalyst (in a concentration of 7 mM), 1.0 eq. of the enecarbamates and 2.0 eq. of the α,α'-diketone and subjected to acidic hydrolysis after 48 h, unless otherwise stated;
[b] The reaction was quenched after 14 days;
[c] The reaction was performed with $Cu(OTf)_2$ instead of $Ni(OTf)_2$;
[d] The ratio corresponds to (**4.44**):(**4.45**).

When enecarbamate (**3.1**) was used together with butane-2,3-dione and the reaction was quenched after 48 h, the expected diketone (**4.42**) was obtained, although in only moderate yield and modest enantiomeric excess (47% yield and 45% *ee*) (entry1, Table 4.14). A somewhat better result was achieved by extending the reaction time to 14 days; under these conditions, diketone (**4.42**) was isolated in modest yield (59%) and with 65% enantiomeric excess (entry 2, Table 4.14). The same trend was observed when enecarbamate (**3.2**) was used in conjunction with butane-2,3-dione: quenching the reaction after 48 h delivered diketone (**4.43**) with a good enantiomeric

excess (75%) but poor yield (20%) whereas if the reaction was allowed to proceed for 14 days a marked improvement in the reaction yield and enantiomeric excess was obtained (90% and 82% *ee*, respectively) (entries 3 & 4, Table 4.14). The use of the $Cu(OTf)_2$-derived catalyst gave consistently lower enantiomeric excesses than the corresponding $Ni(OTf)_2$ catalyst (35% *ee versus* 45% *ee* for enecarbamate (**3.1**) and 38% *ee versus* 75 % *ee* for enecarbamate (**3.2**), respectively) (entry 5 *versus* entry 1 and entry 6 *versus* entry 3, respectively, Table 4.14). The reaction of the unsymmetrical pentane-2,3-dione with enecarbamate (**1.37**) was also examined. In this case a dramatic increase in the overall yield of the addition was observed when the reaction was allowed to run for 14 days: a 19% overall yield for a 48 h reaction increased to >99% overall yield for the analogous 14 days reaction. However, no corresponding increase in the enantiomeric excess of the major isomer of (**4.44**) was observed and, in fact, the enantiomeric excess of the minor regioisomer (**4.45**) was reduced by almost 20%. Furthermore, the regioselectivity of the addition was also somewhat reduced for longer reaction times (8.5:1 *versus* 7.0:1). (entry 8 *verus* entry 9, Table 4.14).

## 4.2.3 – Mechanistic Considerations

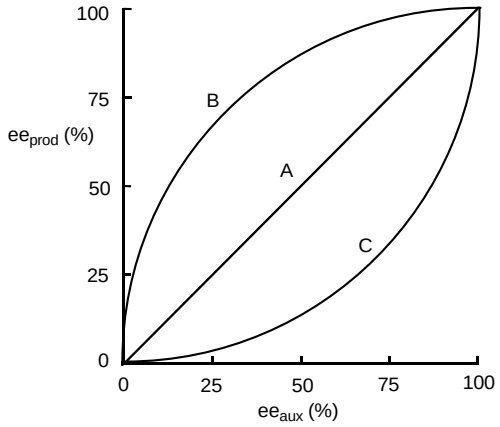
The striking effects that the catalyst loading and concentration have on the reaction yield and enantioselectivity (*vide supra*, Table 4.13) suggest a complex reaction mechanism, possibly due to the formation of dimeric or oligomeric catalyst structures. A simple way to detect and discuss aggregation phenomenon in asymmetric catalysis is through the evaluation of the so-called non-linear effects (NLEs).

### 4.2.3.1 – NLEs in Asymmetric Catalysis: A Brief Overview

The term NLEs refers to reactions where the product enantiomeric excess is not proportional to the enantiomeric purity of the chiral ligand used.[4.20] Accordingly, if one plots the enantiomeric excess of the product of a certain asymmetric reaction as a function of the enantiomeric excess of the required chiral auxiliary, three basic scenarios may be envisioned to arise: the linear correlation, defined by Equation 4.1 is the intuitively expected result whereas the curves B and C represent NLEs cases. The

[4.20] (a) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430. For some reviews, see: (b) Girard, C.; Kagan, H. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 2922. (c) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997. (d) Kagan, H. B. *Adv. Synth. Catal.* **2001**, *343*, 227.

convex curve B represents a situation where the product is always formed with higher enantioselectivity that what is predicted by Equation 4.1 and hence we talk of a positive non-linear effect ((+)-NLE). The opposite applies to the concave curve C and in those cases we refer to a negative non-linear effect ((-)-NLE) (Figure 4.2).




**Curve A**:

$$ee_{product} = ee_0 ee_{ligand}$$ **Equation 4.1**

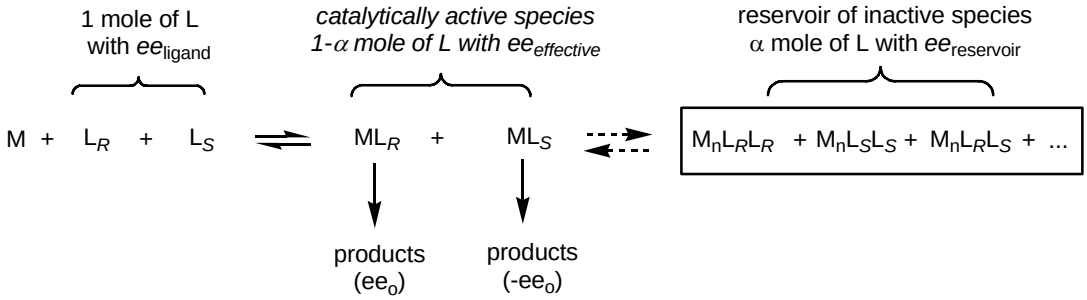
$ee_{product}$: enantiomeric excess of product
$ee_{ligand}$: enantiomeric excess of ligand
$ee_0$: enantiomeric excess of product for $ee_{ligand}$ = 100%

**Curve B**: (+)-NLE (also called asymmetric amplification)

**Curve C**: (-)-NLE (also called asymmetric depletion)

**Figure 4.2** Basic types of NLEs in asymmetric catalysis.

Kagan and co-workers developed several mathematical models to describe NLEs in asymmetric catalysis.[4.20a] One of the simplest models developed, the reservoir model, assumes that part of the chiral ligand (of initial enantiomeric excess $ee_{ligand}$) may be involved in the competitive formation of catalytically inactive complexes in addition to the actual catalysts. A formulation of this model as applied to the case where the competent catalysts are of the form ML, where M stands for a metal centre and L for a chiral ligand, is shown in Scheme 4.11.




**Scheme 4.11** The reservoir model in NLE.

Accordingly, a one-ligand system, consisting of enantiopure complexes $ML_R$ and $ML_S$, which are the active catalysts, and a pool of complexes not directly involved in the catalytic cycle (*e.g.*, the homochiral $ML_RL_R$ and $ML_SL_S$ and the meso $ML_RL_S$

complexes, the dimeric species $(ML_R)(ML_R)$, $(ML_S)(ML_S)$ and $(ML_R)(ML_S)$, *etc.*) are in competition with each other. The two systems may or may not be interconnected by an equilibrium.

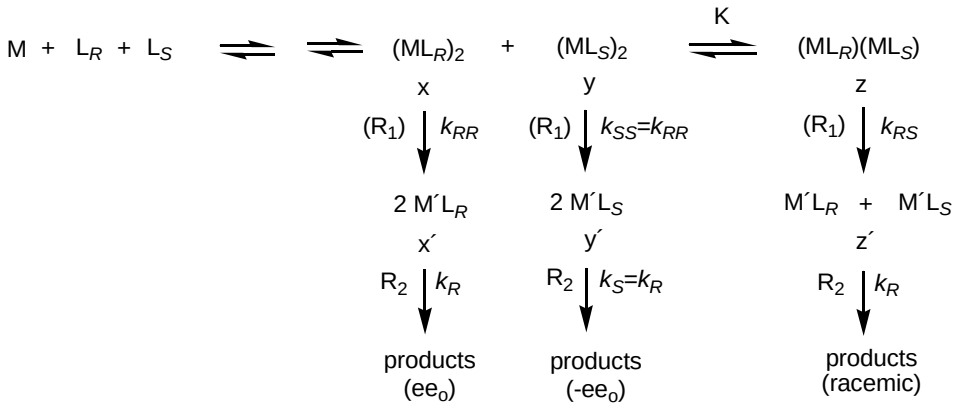
Because the chiral ligand can be stored in the form of unproductive complexes (*i.e.*, in "a reservoir"), the enantiomeric excess of the ligand entering the catalytic cycle may be different from its initial value. Thus, if $\alpha$ is the mole fraction of chiral ligand which is stored in the reservoir and $ee_{\text{reservoir}}$ and $ee_{\text{effective}}$ are the enantiomeric excesses of the chiral ligand which is in the reservoir and involved in the catalytic cycle, respectively, then it can be establish that $ee_{\text{effective}}$ is given by Equation 4.2,

$$ee_{effective} = \frac{ee_{ligand} - \alpha ee_{reservoir}}{1-\alpha} \qquad \textbf{Equation 4.2}$$

and therefore the enantiomeric excess of the product ($ee_{\text{product}}$) is given by Equation 4.3.

$$ee_{product} = ee_0 ee_{effective} = ee_0 \frac{ee_{ligand} - \alpha ee_{reservoir}}{1-\alpha} \qquad \textbf{Equation 4.3}$$

An alternative model to describe NLE in systems where the active catalyst is of the ML form, the so-called $(ML)_2$ model, is shown in Scheme 4.12. This variation of the simpler $ML_2$ model assumes that three dimeric species, two homochiral complexes $(ML_R)_2$ and $(ML_S)_2$ and a heterochiral complex $(ML)_R(ML)_S$, are first established in solution in the absence of the reactants.




**Scheme 4.12** The $(ML)_2$ model in NLE.

At any fixed amount of the chiral ligands $L_R$ and $L_S$ (*i.e.*, for a given $ee_{ligand}$), a steady state exists for the concentrations of these dimers in the mixture, in amounts x, y and z, respectively, which are related by means of the equilibrium constant *K*. The dimeric species are assumed to dissociate irreversibly, eventually with the intervention of a reactant $R_1$, into the catalytically competent species, the monomeric complexes $M'L_R$ and $M'L_S$. Upon reaction with a (second) reactant $R_2$ the product is then formed. Racemic product is obtained from the heterochiral dimer pathway whereas enantiomeric products are produced from the two enantiopure dimers pathways in enantiomeric excesses $ee_o$ and $-ee_o$. All reactions are assumed to be *pseudo*-zero order in substrate and *pseudo*-first order in the complexes concentration. For the cases where the rate limiting step is either the dissociation of the dimeric complexes (i.e., $k_R >> k_{RR}$) or the formation of the product (i.e., $k_{RR} >> k_R$), the enantiomeric excess of the resulting product ($ee_{product}$) is given by Equation 4.4.

$$ee_{product} = ee_o ee_{ligand} \frac{1+\beta}{1+g\beta} \qquad \textbf{Equation 4.4}$$

where the two new parameters, *g* and $\beta$, are given by Equation 4.5 and Equation 4.6, respectively.

$$g = \frac{k_{RS}}{k_{RR}} \qquad \textbf{Equation 4.5}$$

$$\beta = \frac{z}{x+y} = \frac{-Kee_{ligand}^2 + \sqrt{-4Kee_{ligand}^2 + K(4+Kee_{ligand}^2)}}{4+Kee_{ligand}^2} \qquad \textbf{Equation 4.6}$$

with

$$ee_{ligand} = \frac{L_R - L_S}{L_R + L_S} \text{ and } K = \frac{z^2}{xy}$$

The parameter *g* expresses the relative reactivities of the hetero and homochiral complexes while $\beta$ defines the relative amounts of the heterochiral and homochiral dimers.

The above models are useful in providing insights about the structure of the active catalytic species as well as the reaction mechanism. The mathematical expressions

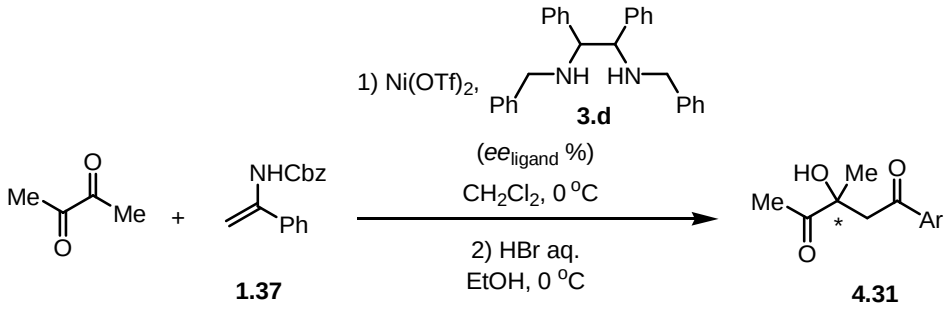
obtained may be used to fit experimental data points and thus quantitative parameters related to the different species that exist in solution may be extracted.

Finally, it should be appreciated that although the two models discussed were treated separately, in practice they may merge or combine. Thus, a set of experimental data points may be fitted with several models and only a detailed kinetic investigation will provide all features of the mechanism and the origin of the NLE.

### 4.2.3.2 - NLEs in the Reaction of Enecarbamate (1.37) to Butane-2,3-Dione Catalyzed by the $C_2$-Symmetric Chiral Ni(II)-diamine (3.d) Complex

The existence of a NLE in the $Ni(OTf)_2$-diamine (**3.d**) catalyzed reaction of enecarbamate (**1.37**) with butane-2,3-dione was investigated. The non-enantiopure catalyst was prepared *in situ* by combining 7 mM stock solutions of racemic and enantiomerically pure (*R*,*R*)-diamine (**3.d**). The results are shown in Table 4.15.

**Table 4.15** Evaluation of NLE in the reaction of enecarbamate (**1.37**) to butane-2,3-dione catalyzed by $Ni(OTf)_2$-diamine (**3.d**).




| Diamine (**3.d**) *ee* (%) | Diketone (**4.31**) *ee* (%) | Diketone (**4.31**) yield (%) |
|---|---|---|
| 10 | 58 | 32 |
| 35 | 78 | 57 |
| 50 | 79 | 52 |
| 77 | 76 | 69 |
| 100 | 76 | 67 |

[a] The reactions were performed in $CH_2Cl_2$ at 0 °C with 10 mol% of the catalyst (in a concentration of 7 mM), 1.0 eq. of enecarbamate (**1.37**) and 2.0 eq. of the $\alpha,\alpha'$-diketone and subjected to acidic hydrolysis after 48 h;

As it can be seen in Figure 4.3, a strong (+)-NLE was observed.

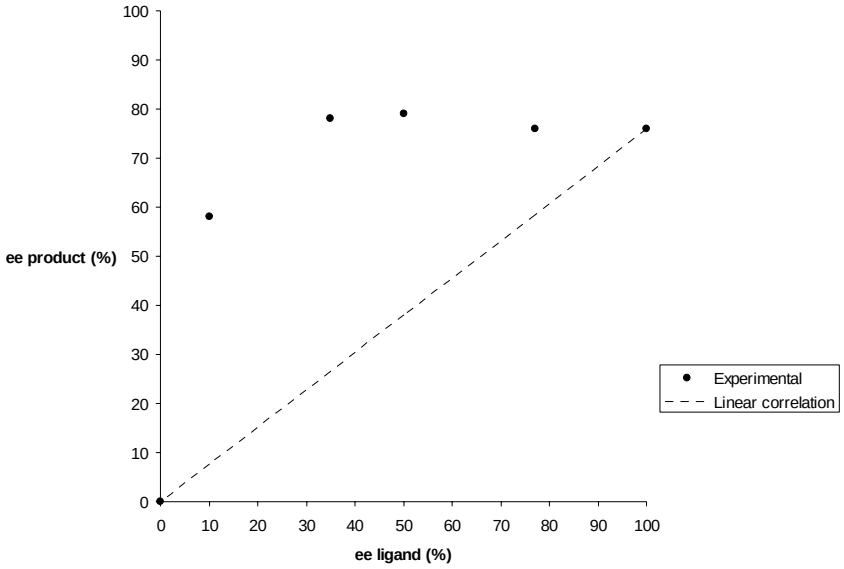



**Figure 4.3** NLE in the reaction of enecarbamate (**1.37**) with butane-2,3-dione catalyzed by $Ni(OTf)_2$-diamine (**3.d**).

These experimental data may be described by Equation 4.3 (*i.e.*, the reservoir model) with $ee_0 = 76\%$, $ee_{reservoir} = 0\%$ and $\alpha = 0.89$ (Figure 4.4). These parameters imply that a racemic, fairly populated reservoir is formed before or, in parallel to, the establishment of the steady state in the catalytic cycle. The simplest way to achieve this is *via* the formation of a thermodynamic stable and kinetically inactive meso complex of the type Ni{[(*S*,*S*)-(**3.d**)][(*R*,*R*)-(**3.d**)]}. If instead Equation 4.4 is used (*i.e.*, the $(ML)_2$ model), the values $ee_0 = 76\%$, $K = 2800$ and $g = 0.01$ give a curve that also fits the experimental results (Figure 4.4). These parameters translate into a large predominance of a heterochiral dimer of the type {Ni[(*S*,*S*)-(**3.d**)]}-{Ni[(*R*,*R*)-(**3.d**)]} which has a very low reactivity ($k_{RS}/k_{RR} \approx 1/100$). This species can therefore act as a trap for the minor enantiomer of the ligand (*i.e.*, a kind of reservoir effect). The more reactive homochiral-enriched dimers left will then afford the active catalysts {Ni[(*S*,*S*)-(**3.d**)]} and {Ni[(*R*,*R*)-(**3.d**)]} with an enantiomeric excess greater than the initial introduced thus resulting in a (+)-NLE.

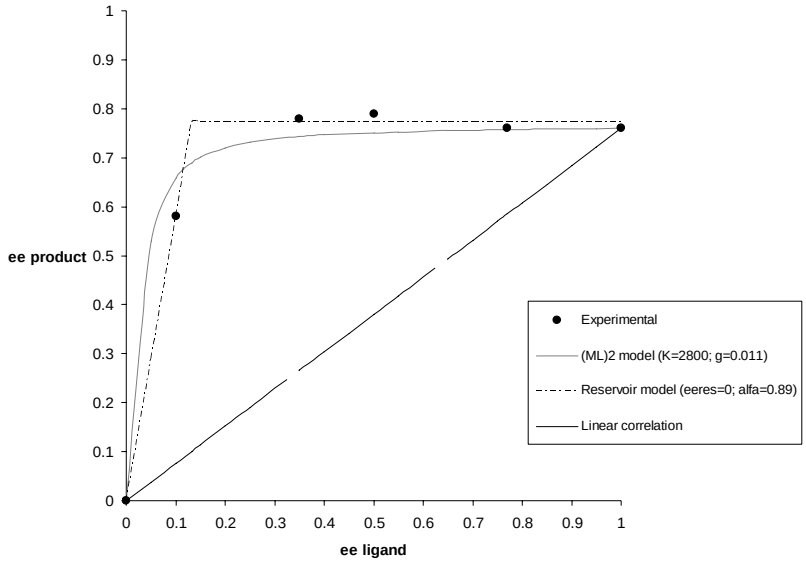



**Figure 4.4** Description of the NLE observed according to the reservoir model and the $(ML)_2$ model.

The influence of the enantiomeric excess of the chiral ligand (**3.d**) on the chemical yield of diketone (**4.41**) was also evaluated (*vide supra*, Table 4.15) and this is shown in Figure 4.5.

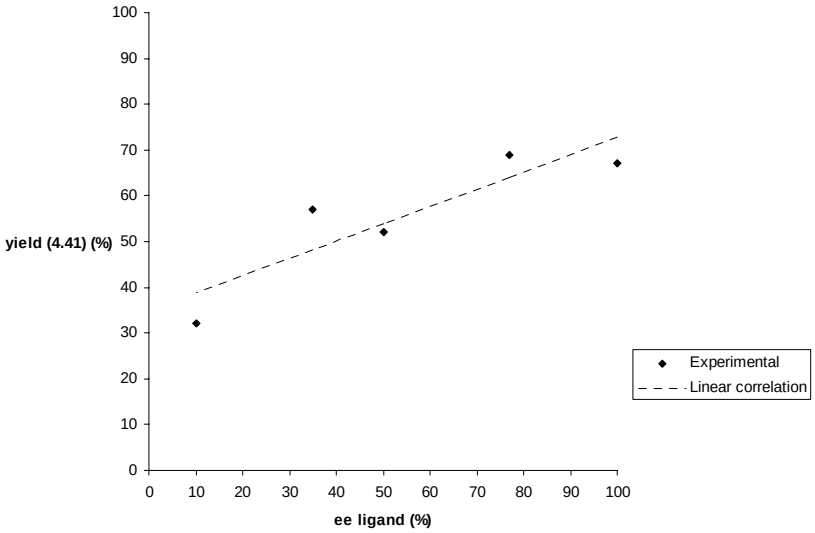


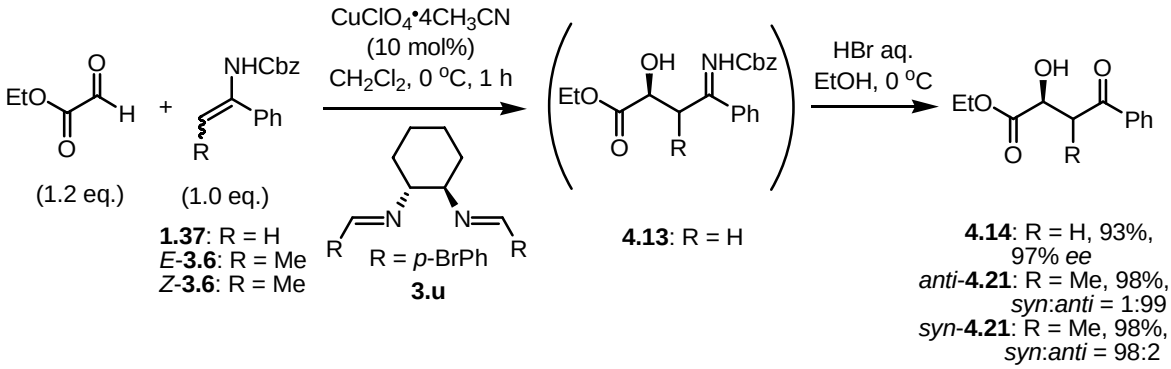

**Figure 4.5** Effect of diamine (**3.d**) *ee* in α,α'-diketone (**4.41**) yield in the reaction of enecarbamate (**1.37**) with butane-2,3-dione catalyzed by $Ni(OTf)_2$-diamine (**3.d**).

As it can be seen there is an approximate linear correlation between these two variables implying that the amount of the active catalysts in solution, presumably {Ni[(*S*,*S*)-(**3.d**)]}$(OTf)_2$ and {Ni[(*R*,*R*)-(**3.d**)]}$(OTf)_2$, increases with the enantiomeric excess of the chiral diamine ligand (**3.d**). This result further supports the preferential formation of the heterochiral complex Ni{[(*S*,*S*)-(**3.d**)][(*R*,*R*)-(**3.d**)]}$(OTf)_2$ and/or the heterochiral dimer {Ni[(*S*,*S*)-(**3.d**)]}·{Ni[(*R*,*R*)-(**3.d**)]}$(OTf)_4$ and that these species are kinetically inactive.

# CHAPTER 5
# Concluding Remarks

The catalytic asymmetric reactions of enecarbamates with *α,α'*-dicarbonyl compounds, particularly ethyl glyoxylate and butane-2,3-dione, were investigated.

It was found that secondary enecarbamates reacted with ethyl glyoxylate in a highly diastereo- and enantioselective manner in the presence of chiral copper(I)-diimine catalysts to give optically active 1,3-hydroxy imines. These intermediates were subjected *in situ* to acid hydrolysis affording the corresponding *β*-hydroxy ketones with excellent optical purity (up to 97% *ee*) and in good to excellent yields (typically >90%). The most effective chiral catalyst found was obtained from $CuClO_4 \cdot 4CH_3CN$ and the $C_2$-symmetric diimine ligand (**3.u**) (Scheme 5.1). The reaction proceeded smoothly even in the presence of only 0.1 mol% of the catalyst.

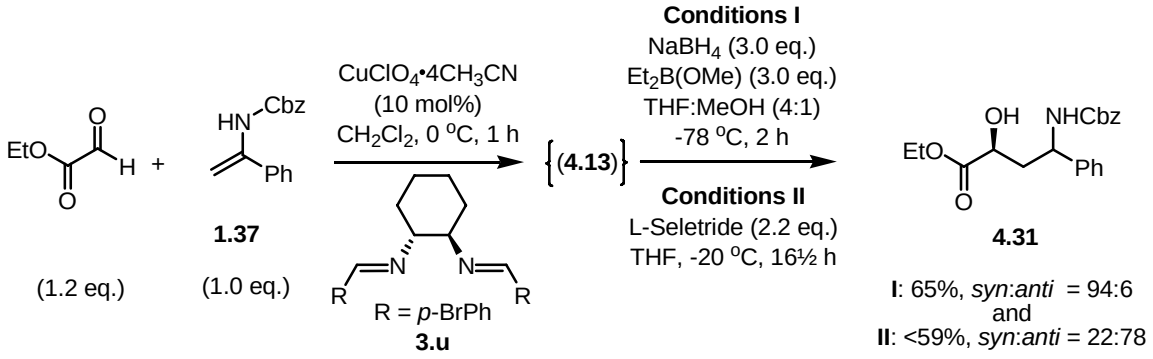



**Scheme 5.1** Examples of the reaction of enecarbamates with ethyl glyoxylate catalyzed by the Cu(I)-diimine (**3.u**) complex.

The relative and absolute configuration of the aldol-type adducts were determined by derivatization. A concerted aza-ene mechanism was proposed based on the stereochemical outcome of the reaction. This process is believed to take place through an envelope transition state where the carbamate proton plays a key role. The observed chiral induction was rationalized by considering a tetrahedral chiral copper(I) centre, where the *Re*-face of the coordinated ethyl glyoxylate is shielded by the chiral ligand and the *Si*-face is left open to be approached by the *Si*-face of the enecarbamate.

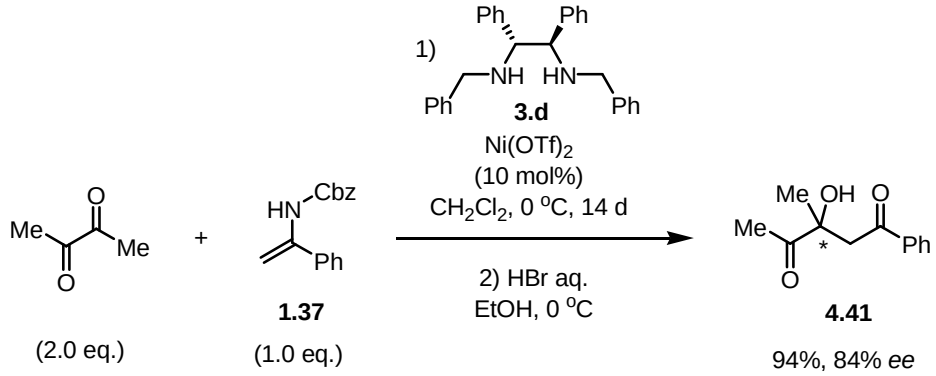
The chiral 1,3-imino alcohol intermediate (**4.13**) was also diastereoselectively reduced *in situ* into the corresponding 1,3-hydroxy carbamate (**4.31**). When chelating type

conditions were used (excess of $NaBH_4$ and $Et_2B(OMe)$) the *syn*-adduct (**4.31**) was obtained in good yield (65%) and high diastereomeric excess (94:6, *syn*:*anti* ratio). On the other hand, the use of L-Selectride delivered the corresponding *anti*-adduct as the major product, but only in moderate yield (<59%) and with modest diastereomeric excess (22:78, *syn*:*anti* ratio) (Scheme 5.2).




**Scheme 5.2** Diastereoselective reductions of enantiopure 1,3-hydroxy imine (**4.13**).

The catalytic asymmetric addition reaction of secondary enecarbamates to *α,α'*-diketones was also accomplished (with limitations, *vide infra*). A novel nickel(II)-based catalyst, obtained from $Ni(OTf)_2$ and the $C_2$-symmetric diamine ligand (**3.d**), afforded the best enantioselectivities. When the symmetric butane 2,3-dione was used and the intermediate *β*-hydroxy imine was subjected *in situ* to acidic hydrolysis, the corresponding tertiary alcohol (**4.41**) was obtained in high yield (94%) and with good enantiomeric excess (84%) (Scheme 5.3).




**Scheme 5.3** Addition reaction of enecarbamate (**1.37**) to butane-2,3-dione catalyzed by the Ni(II)-diamine (**3.d**) complex.

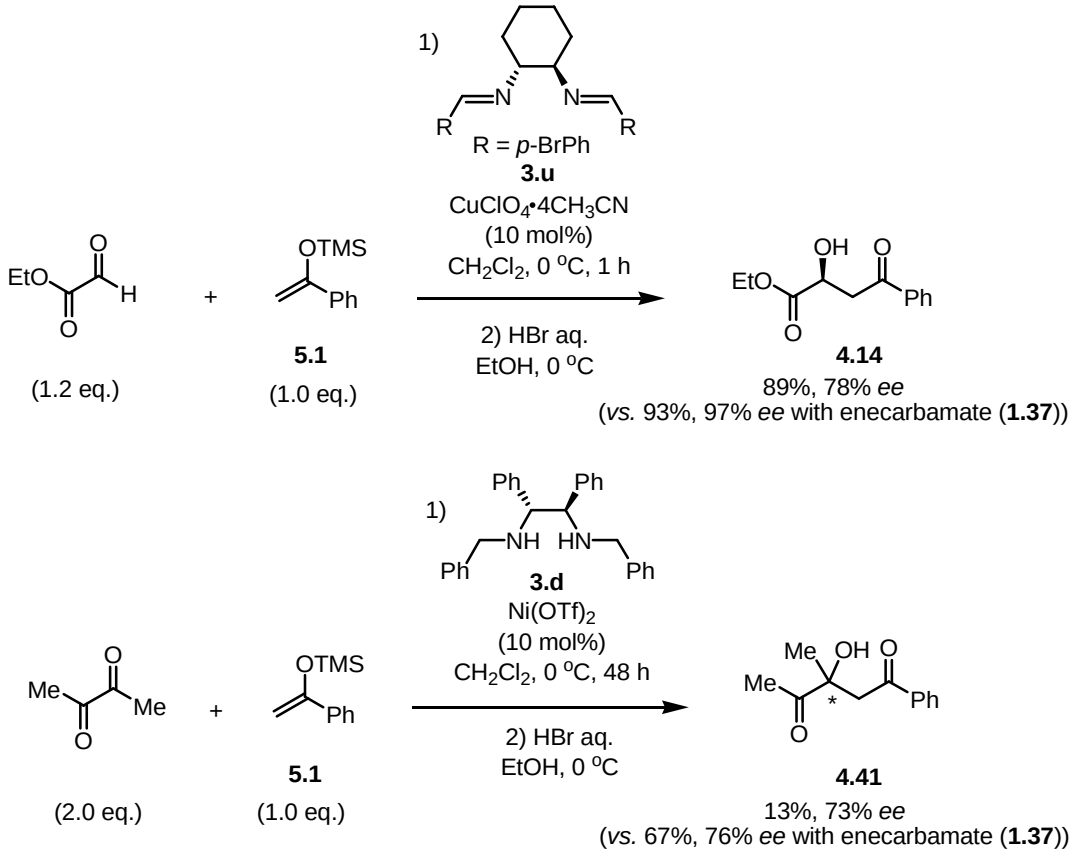
However, the use of $\alpha,\alpha'$-diketones is, at the present, limited by the very low turnover frequency of the catalytic cycle: very long reaction times, typically around 14 days, were required for obtaining high yields and good enantioselectivities. Further studies are thus necessary to obtain a more efficient catalytic system.

It was also found that the addition reaction of enecarbamate (**1.37**) to butane-2,3-dione catalyzed by a non-enantiopure Ni(II)-diamine (**3.d**) complex shows a strong (+)-NLE. The observed deviations to linearity were ascribed to the preferential formation of heterochiral complexes Ni{[(*S*,*S*)-(**3.d**)][(*R*,*R*)-(**3.d**)]}$(OTf)_2$ and/or the heterochiral dimer {Ni[(*S*,*S*)-(**3.d**)]}·{Ni[(*R*,*R*)-(**3.d**)]}$(OTf)_4$, which are likely to be kinetically inactive species. Semi-quantitative data that supports these assumptions was obtained by using the reservoir and the $(ML)_2$ models.

Based on the type of products obtained, namely $\beta$-hydroxy ketones and $\beta$-hydroxy carbamate, it can be concluded that enecarbamates represent an alternative to the more commonly used aldol approach,[5.1] namely the silyl enol ether-based Mukaiyama variation,[5.1b,c] eventually followed by a reductive amination step. Thus an important question is whether a substantial synthetic benefit arises from the use of enecarbamates as nucleophiles. Whereas the latter are typically crystalline solids which can be stored at room temperature without special precautions, their preparation can be difficult, often requiring more than one step, harsh conditions and a final purification by flash chromatography. On the other hand, silyl enol ethers are readily synthesized on scale in one step from commercial materials in good yield and conveniently purified by distillation; however, usually they do not store well and thus are required to be prepared *in situ*.[5.1b,c] In order to try differentiating between the use of enecarbamates and enolsilanes from a reactivity point of view, the TMS-enolate of acetophenone (**5.1**) was prepared[5.2] and subjected to the conditions that afforded the best results when enecarbamate (**1.37**) was used (Scheme 5.4).

[5.1] For selected aldol-reactions reviews, see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. *Top. Stereochem.* **1982**, *13*, 1. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (c) Mukaiyama, T.; Kobayashi, S. *Org. React.* **1994**, *46*, 1. (d) Heathcock, C. H. in "Comprehensive Organic Synthesis" (Trost, B. M., Fleming, I. ed.) **1991**, *1*, 133, 181, 239, 301, Pergamon Press, New York. (e) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (f) Carreira, E. M. in "Catalytic Asymmetric Synthesis" ($2^{nd}$ Edition) (Ojima, I. ed.), **2000**, 513, Wiley-VCH, New York.

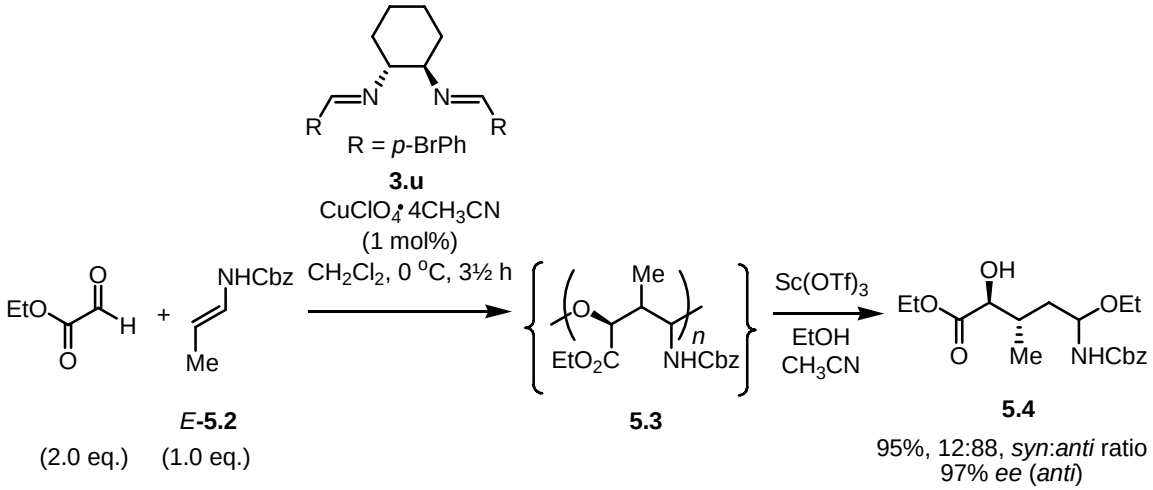
[5.2] For a general reference see: Colvin, E. W. in "Silicon Reagents in Organic Synthesis" **1988**, Academic, New York.




**Scheme 5.4** Comparison between enecarbamate (**1.37**) and enolsilane (**5.1**) in the catalyzed reactions with ethyl glyoxylate and butane-2,3-dione.

These preliminary results suggest that for the ethyl glyoxylate case there is no noteworthy advantage in using enecarbamate (**1.37**) over enolsilane (**5.1**): the *β*-hydroxy ketone (**4.14**) was obtained with comparable yields (93% *versus* 89%, respectively) and although with the latter a somewhat lower enantioselectivity was obtained (97% *ee versus* 78% *ee*, respectively), probably some fine-tuning of the Mukaiyama reaction conditions would lead to an increase in the enantioselectivity. In contrast to the ethyl glyoxylate case, the use of enecarbamate (**1.37**) with butane-2,3-dione proved to be considerably superior to the Mukaiyama-type conditions: the chiral tertiary alcohol (**4.41**) was isolated in only 13% yield when silyl enol ether (**5.1**) was used whereas enecarbamate afforded the same product in 67% yield; the enantioselectivity was similar for both cases (73% *ee* and 76% *ee*, respectively). Hence, the use of enecarbamates over silyl enol ethers can in deed be beneficial, although there are situations where the distinction between the two types of nucleophiles is not clear-cut and the final choice will be based on a personal bias.

Finally it should be mentioned that while this writing was in progress, a new development concerning the use of enecarbamates in asymmetric catalysis was reported. Kobayashi and co-workers found that enecarbamates derived from aldehydes, such as (**5.2**), can react diastereo- and enantioselectively with ethyl glyoxylate in the presence of the Cu(I)-diamine (**3.u**) to give a polymeric structure, presumably (**5.3**), which can be converted *in situ* into the corresponding *N*,*O*-acetal monomer (**5.4**) by treatment with a catalytic amount of $Sc(OTf)_3$ in EtOH (Scheme 5.5).[5.3]




**Scheme 5.5** Addition reaction of aldehyde-derived enecarbamate *E*-(**5.2**) to ethyl glyoxylate catalyzed by the Cu(I)-diimine (**3.u**) complex.

In conclusion, enecarbamates are useful, versatile and atom-economic nucleophiles that can be use in asymmetric catalysis and which potential only now is starting to be unveiled.

[5.3] Matsubara, R.; Kawai, N.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 3814.

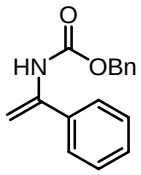
# CHAPTER 6
# Experimental

## 6.1 - General

All moisture and air sensitive reactions were carried out under an argon atmosphere using flame-dried glassware. Reaction solvents were distilled prior to use by standard procedures. $^{1}$H- and $^{13}$C-NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400 or JNM-LA500 spectrometer in $CDCl_3$ unless otherwise stated. Chemical shifts (δ) are reported in ppm. Tetramethylsilane (TMS) (δ = 0) and $CDCl_3$ (δ = 77.0) were used as internal standards for $^{1}$H- and $^{13}$C-NMR, respectively. Coupling constants (*J*) are given in Hertz (Hz). Multiplicities of peaks are reported in the following way: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad), app (apparent) and combinations of these. IR spectra were measured with a JASCO FT/IR-610 spectrometer. Optical rotations were measured with a JASCO P-1010 polarimeter and the concentration (*c*) is given in g *per* 100 mL. Analytical high performance liquid chromatography (HPLC) was performed using the following apparatus: SHIMADZU LC-10AT (liquid chromatography), SHIMADZU SPD-10A (UV detector) and SHIMADZU C-R6A Chromatopac. Gas chromatography (GC) and mass spectrometry (MS) analysis was carried out using the following apparatuses: SHIMADZU GC-17A, SHIMADZU GCMS-QP5050A or BRUKER DIALATONICS® BIOTOF® II machine. Melting points of crystalline materials are uncorrected and were determined on a YAZAWA BY-1 apparatus. Merk silica gel 60 (40-63 μm, 230-400 mesh) was used for column chromatography purification. Preparative thin layer chromatography (PTLC) was carried out using Wakogel B-5F. Materials to be separated by PTLC are applied as long streaks, developed and recovered by scraping the adsorbent from the plate and eluting with EtOAc. Unless otherwise stated, commercially available reagents, purchased from Tokyo Kasei Kogyo (TCI) and Aldrich and Fluka, were used without further purification. All compounds for which HRMS was performed exhibited clean $^{1}$H-NMR and showed only one spot on TLC. Molecular sieves were dried at 150-160 $^{o}$C for at least 12 h and then allowed to reach room temperature under argon. Commercial NaH (as a 60% dispersion in oil) is washed with pentane (2 portions that cover the amount used) and the last traces of pentane are removed under high vacuum.

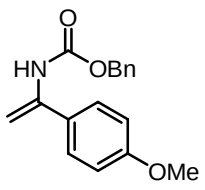
## 6.2 - Preparation of Enecarbamates and Chiral Ligands

**General procedure for the preparation of aromatic enecarbamates (GP 1):**[6.1]
The aromatic nitrile (63.0 mmol, 1.0 eq.) was added to a solution of the appropriated Grignard reagent in THF (69.3 mmol, 1.1 eq.) at ice bath temperature. The obtained solution was allowed to reach room temperature, stirred for ½ h and then refluxed for 1 h. The resulting solution was cooled to ice bath temperature and the chloroformate reagent (75.6 mmol, 1.2 eq.) was dropwise added. After stirring at 0 °C for ½ h, the solution was allowed to reach room temperature, stirred for further 2 h and then quenched at ice bath temperature by addition of $H_2O$ (40 mL). After separation of the layers, the aqueous layer was extracted with EtOAc (2 portions of 40 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and the solvent was removed under vacuum affording a yellow oil which was purified by column chromatography (typically using as eluent hexane:EtOAc, 8:1). The obtained enecarbamates were then taken in petroleum ether (15 mL) and the obtained suspension was stirred for approx. 5 h.; filtration and drying under vacuum to remove the last traces of solvent finally afforded the pure enecarbamates.




**(1-Phenyl-vinyl)-carbamic acid benzyl ester (1.37)**

Obtained in 48%; mp 69.4-69.5 °C; $^1$H-NMR ($CDCl_3$) δ 4.96 (s, 1H), 5.16 (s, 2H), 5.63 (s, 1H), 6.33 (s, 1H), 7.25-7.45 (m, 10H); $^{13}$C-NMR ($CDCl_3$) δ 67.0, 99.6, 126.0, 128.3, 128.5, 128.6, 128.7, 136.0, 138.1, 140.5, 153.7; IR (neat) 3310, 3060, 3033, 1739, 1701, 1634, 1523, 1452, 1227, 1125, 1063, 857, 772, 740, 696, 596 cm$^{-1}$; Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.77; H, 6.16; N, 5.52.

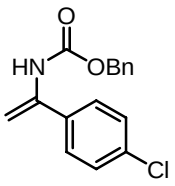



**[1-(4-Methoxy-phenyl)-vinyl]-carbamic acid benzyl ester (3.1)**

Obtained in 43%; mp 54.7-54.8 °C; $^1$H-NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.89 (d, 1H, $J$ = 1.0 Hz), 5.18 (s, 2H), 5.54 (s, 1H), 6.26 (s,1H), 6.85-6.90 (m, 2H), 7.30-7.40 (m, 7H); $^{13}$C-NMR ($CDCl_3$) δ 55.3, 66.9, 98.4, 113.9, 127.2, 128.3, 128.5, 130.6, 136.0, 140.1, 153.7, 160.0; IR (neat) 3330, 1736, 1632, 1608, 1509, 1456, 1219, 1179, 1126, 1063, 1030, 834, 742, 698 cm$^{-1}$; HRMS (EI); Exact mass calcd. for $C_{17}H_{17}NO_3$ $[M]^+$,

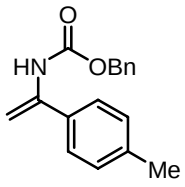
[6.1] Suen, Y. H.; Horeau, A.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1965**, *5*, 1454.

283.1208. Found 283.1208; Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.84; H, 6.09; N, 4.91.



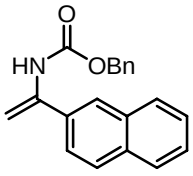

**[1-(4-Chloro-phenyl)-vinyl]-carbamic acid benzyl ester (3.2)**

Obtained in 47%; mp 79.0-79.1 $^oC$; $^1H$-NMR ($CDCl_3$) δ 4.96 (s, 1H), 5.17 (s, 2H), 5.59 (s, 1H), 6.25 (s,1H), 7.28-7.43 (m, 9H); $^{13}C$-NMR ($CDCl_3$) δ 67.1, 100.6, 127.3, 128.3, 128.4, 128.6, 128.8, 134.6, 135.8, 136.5, 139.7, 153.6; IR (neat) 3299, 1699, 1532, 1239, 1059, 838, 741, 696 $cm^{-1}$; HRMS (EI); Exact mass calcd for $C_{16}H_{14}NO_2$ $[M]^+$, 287.0713. Found 287.0708. Anal. Calcd. for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87. Found: C, 66.53; H, 5.02; N, 4.91.



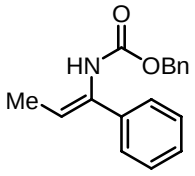

**(1-*p*-Tolyl-vinyl)-carbamic acid benzyl ester (3.3)**

Mp 52.8-53.0 $^oC$; $^1H$-NMR ($CDCl_3$) δ 2.34 (s, 3H), 4.93 (s, 1H), 5.16 (s, 2H), 5.58 (s,1H), 6.30 (s, 1H), 7.40 (appd, 2H, $J$ = 7.8 Hz), 7.25-7.40 (m, 7H); $^{13}C$-NMR ($CDCl_3$) δ 21.1, 66.9, 98.8, 125.8, 128.3, 128.5, 129.3, 135.3, 136.0, 138.7, 140.4, 153.7; IR (neat) 3398, 3327, 3032, 1736, 1361, 1508, 1454, 1383, 1219, 1063, 955, 825, 735 $cm^{-1}$; LRMS (FAB) *m/z* = 268 $[M+H]^+$; Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.20; H, 6.48; N, 5.21.



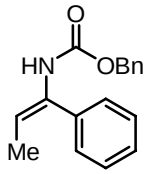

**(1-Naphthalen-2-yl-vinyl)-carbamic acid benzyl ester (3.4)**

Mp 100.3-101.5 $^oC$; $^1H$-NMR ($CDCl_3$) δ 5.11 (s, 1H), 5.19 (s, 2H), 5.72 (s, 1H), 6.45 (s,1H), 7.30-7.60 (m, 8H), 7.76-7.86 (m, 4H); $^{13}C$-NMR ($CDCl_3$) δ 67.1, 100.4, 124.0, 124.7, 126.5, 127.6, 128.2, 128.3, 128.4, 128.6, 133.1, 133.3, 135.3, 135.9, 140.5, 153.8; IR (neat) 3282, 3046, 1701, 1622, 1527, 1226, 1106, 1064, 968, 884, 827, 694, 583 $cm^{-1}$; HRMS (EI); Exact mass calcd for $C_{20}H_{17}NO_2$ $[M]^+$, 303.1259. Found 303.1251. Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.49; H, 5.82; N, 4.64.



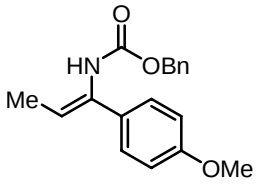
**(*Z*)-(1-Phenyl-propenyl)-carbamic acid benzyl ester (3.6)**

Obtained in 14%; mp 73.5-74.0 °C; $^1$H-NMR ($CDCl_3$) δ 1.79 (d, 3H, *J* = 6.8 Hz), 5.13 (s, 2H), 5.79 (q, 1H, *J* = 6.8 Hz), 6.00 (brs, 1H), 7.00-7.62 (m, 10H); $^{13}$C-NMR ($C_6D_6$) δ 13.5, 67.0, 119.5, 126.0, 127.7, 128.5, 128.5, 135.0, 137.1, 139.2; IR (neat) 3385, 3296, 3032, 2941, 1701, 1498, 1452, 1399, 1329, 1225, 1089, 1018, 916, 824, 760, 695 cm$^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1339.



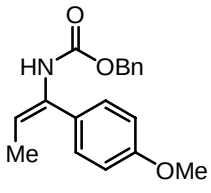
**(*E*)-(1-Phenyl-propenyl)-carbamic acid benzyl ester (3.6)**

Obtained in 31%; mp 63.9-64.0 °C; $^1$H-NMR ($CDCl_3$) δ 1.70 (d, 3H, *J* = 7.3 Hz), 5.11 (s, 2H), 5.90-6.25 (brs, 2H), 7.20-7.50 (m, 10H); $^{13}$C-NMR ($C_6D_6$) δ 13.7, 66.7, 112.0, 128.0, 128.1, 128.5, 128.5, 128.6, 129.1, 134.6, 137.0, 137.2, 153.9; IR (neat) 3398, 3316, 3032, 2938, 1713, 1516, 1449, 1393, 1328, 1213, 1137, 1033, 922, 835, 771, 739, 699, 587 cm$^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1347.



**(*Z*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid benzyl ester (3.7)**

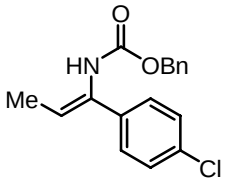
Obtained in 9%; mp 110-110.5 °C; $^1$H-NMR ($CDCl_3$) δ 1.77 (d, 3H, *J* = 6.9 Hz), 3.80 (s, 3H), 5.14 (s, 2H), 5.68 (q, 1H, *J* = 6.9 Hz), 5.96 (brs, 1H), 6.84 (appd, 2H, *J* = 8.8 Hz), 7.32 (m, 7H); $^{13}$C-NMR ($C_6D_6$) δ 13.5, 54.8, 66.9, 114.0, 117.6, 127.2, 128.5, 131.8, 134.6, 137.2, 154.1, 159.8; IR (neat) 3305, 3039, 2945, 2843, 1709, 1611, 1509, 1452, 1400, 1334, 1294, 1247, 1176, 1089, 1029, 820, 742, 699, 590 cm$^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{18}H_{20}NO_3$ $[M+H]^+$, 298.1443. Found 298.1435.



**(*E*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid benzyl ester (3.7)**

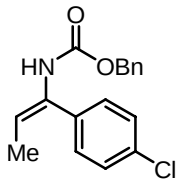
Obtained in 33%; mp 66.0-66.5 °C; $^1$H-NMR ($CDCl_3$) δ 1.69 (d, 3H, *J* = 7.1 Hz), 3.82 (s, 3H), 5.11 (s, 2H), 5.80-6.15 (m, 2H), 6.85-6.95 (m, 2H), 7.20-7.50 (m, 7H); $^{13}$C-NMR ($C_6D_6$) δ 13.8, 54.7, 66.6, 111.1, 114.0, 128.1, 128.5, 128.6, 129.5, 130.3, 134.4, 137.1, 153.9, 159.7; IR (neat) 3323, 3033, 2941, 2843, 1719, 1609, 1509, 1296, 1247, 1177, 1135, 1027, 840, 739, 697

$cm^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{18}H_{20}NO_3$ $[M+H]^+$, 298.1443. Found 298.1452.



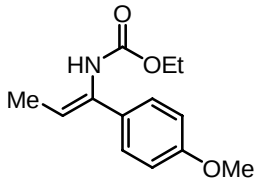

**(*Z*)-[1-(4-Chloro-phenyl)-propenyl]-carbamic acid benzyl ester (3.8)**

Obtained in 12%; mp 95.2-95.3 °C; $^1$H-NMR ($C_6D_6$) δ 1.48 (brs, 3H), 5.02 (brs, 2H), 5.20-5.90 (brs, 2H), 6.60-7.40 (m, 9H); $^{13}$C-NMR ($C_6D_6$) δ 13.4, 67.1, 119.8, 127.2, 128.3, 128.6, 133.4, 134.0, 136.9, 137.7, 153.8; IR (neat) 3292, 3033, 2947, 1706, 1589, 1494, 1398, 1327, 1299, 1094, 1016, 819, 741, 697 $cm^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{17}H_{17}ClNO_2$ $[M+H]^+$, 302.0948. Found 302.0936.



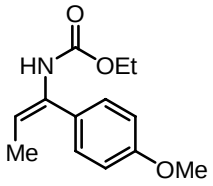

**(*E*)-[1-(4-Chloro-phenyl)-propenyl]-carbamic acid benzyl ester (3.8)**

Obtained in 33%; mp 71.2-71.3 °C; $^1$H-NMR ($C_6D_6$) δ 1.44 (d, 3H, $J$ = 7.4 Hz)), 5.02 (s, 2H), 5.47 (brs; 1H), 6.12 (brs, 1H), 6.70-6.80 (m, 2H), 6.95-7.25 (m, 7H); $^{13}$C-NMR ($C_6D_6$) δ 13.5, 66.8, 128.6, 128.6, 128.7, 130.4, 133.5, 133.8, 135.4, 136.9, 153.7; IR (neat) 3398, 3309, 3033, 2941, 1708, 1595, 1517, 1497, 1458, 1393, 1327, 1219, 1138, 1093, 1034, 836, 740, 701 $cm^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{17}H_{17}ClNO_2$ $[M+H]^+$, 302.0948. Found 302.0943.



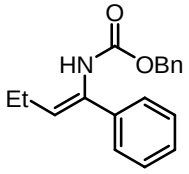

**(*Z*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid ethyl ester (3.9)**

Obtained in 9%; mp 57.1-57.2 °C; $^1$H-NMR ($CDCl_3$) δ 1.25 (brs, 3H), 1.75 (d, 3H, $J$ = 7.1 Hz), 3.78 (s, 3H), 4.13 (q, 2H, $J$ = 7.1 Hz), 5.66 (q, 1H, $J$ = 7.1 Hz), 5.88 (brs, 1H), 6.80-6.85 (m, 2H), 7.28-7.36 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 13.4, 14.5, 55.2, 61.2, 113.6, 117.4, 126.7, 131.1, 133.9, 159.2; IR (neat) 3301, 2979, 1703, 1609, 1510, 1376, 1329, 1245, 1178, 1099, 1037, 824, 774, 594, 448 $cm^{-1}$; HRMS (EI); Exact mass calcd. for $C_{13}H_{17}NO_3$ $[M]^+$, 235.1208. Found 235.1204. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.21; H, 7.32; N, 5.95.



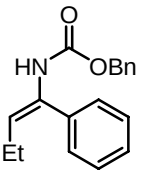
**(*E*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid ethyl ester (3.9)**

Obtained in 24%; mp 52.3-52.6 °C; $^1$H-NMR ($CDCl_3$) δ 1.11 (t, 3H, *J* = 7.1 Hz)), 1.57 (d, 3H, *J* = 7.3 Hz), 3.70 (s, 3H), 4.01 (q, 2H, *J* = 7.1 Hz), 5.70-5.95 (m, 2H), 6.73-6.80 (m, 2H), 7.10-7.16 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 13.7, 14.5, 55.2, 60.8, 111.6, 113.6, 129.1, 129.9, 133.7, 154.3, 159.1; IR (neat) 3319, 2980, 1715, 1608, 1511, 1382, 1293, 1247, 1175, 1138, 1037, 836, 614, 499 cm$^{-1}$; HRMS (EI); Exact mass calcd. for $C_{13}H_{17}NO_3$ $[M]^+$, 235.1208. Found 235.1201.



**(*Z*)-(1-Phenyl-but-1-enyl)-carbamic acid benzyl ester (3.11)**

Mp 60.3-60.8 °C; $^1$H-NMR ($C_6D_6$) δ 0.89 (t, 3H, *J* = 7.1 Hz), 2.03 (brs, 2H), 5.04 (s, 2H), 5.30-5.55 (m, 2H), 7.00-7.25 (m, 8H), 7.28-7.36 (m, 2H); $^{13}$C-NMR ($C_6D_6$) δ 13.6, 21.6, 67.0, 126.1, 126.8, 127.4, 128.1, 128.5, 128.6, 133.5, 137.1, 139.2; IR (neat) 3294, 3033, 2961, 2876, 1705, 1498, 1458, 1400, 1334, 1223, 1092, 1026, 753, 691 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$, 282.1494. Found 282.1495.



**(*E*)-(1-Phenyl-but-1-enyl)-carbamic acid benzyl ester (3.11)**

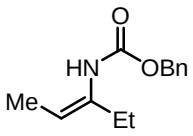
Mp 55.2-55.7 °C; $^1$H-NMR ($C_6D_6$) δ 0.87 (t, 3H, *J* = 7.4 Hz), 1.99 (quint, 3H, *J* = 7.4 Hz), 5.01 (s, 2H), 5.56 (brs, 1H), 6.26 (brs, 1H), 6.95-7.25 (m, 10H); $^{13}$C-NMR ($C_6D_6$) δ 15.1, 21.0, 66.6, 118.8, 126.4, 126.9, 128.2, 128.5, 128.6, 128.6, 129.0, 133.6, 137.1, 137.5, 153.6; IR (neat) 3398, 3319, 3032, 2962, 2876, 1723, 1514, 1454, 1367, 1327, 1219, 1134, 1039, 984, 922, 857, 743, 698 cm$^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{18}H_{20}NO_2$ $[M+H]^+$, 282.1494. Found 282.1481.

**General procedure for the preparation of aliphatic enecarbamates (GP 2):**[6.2]

To a solution of $NaN_3$ (1.68 g, 25.8 mmol) in $H_2O$ (12 mL) was added a solution of the acid chloride (21.47 mmol) in THF (7 mL) dropwise at 0 °C. The mixture was vigorously stirred overnight, after which $Et_2O$ (15 mL) was added. After separation of the layers, the organic layer was washed with a saturated aqueous solution of $Na_2CO_3$ (10 mL) and brine (10 mL) sequentially. The $Et_2O$ was removed under reduced

[6.2] Overman, L. E.; Taylor, G. F.; Jessup, P. J. *Tetrahedron Lett.* **1976**, *36*, 3089.

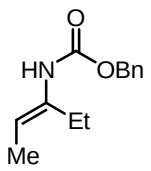
pressure (300 mmHg) (**CAUTION**: this procedure should be carried out behind a safety shield as occasionally explosions occurred) to give the crude acyl azide in THF. This solution was added very slowly over 15 h to refluxing THF (10 mL) at 80 $^{o}$C. After completion of the addition, the mixture was stirred at 80 $^{o}$C until evolution of $N_2$ gas stopped (approx. 2 h). The mixture was allowed to reach room temperature and the THF was evaporated (100 mmHg). The residue was distilled (65 $^{o}$C , 100 mmHg, 2 times) affording the corresponding isocyanate. Benzyl alcohol (1.11 g, 10.0 mmol) was added dropwise at -78 $^{o}$C. The frozen reaction mixture was allowed to warm to room temperature over 6 h and was stirred until no more starting isocyanate was detected by NMR analysis (typically 3 days). The mixture was purified by column chromatography or preparative thin layer chromatography to deliver the pure enecarbamate.




**(*Z*)-(1-Ethyl-propenyl)-carbamic acid benzyl ester (3.13)**

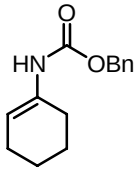
To a stirred solution of angelic methyl ester (9.4 g, 83 mmol) in MeOH and $H_2O$ (1:1, 50 mL) was added solid $LiOH{\cdot}H_2O$ (3.8 g, 91 mmol). The resulting solution was refluxed for 4 h, and then cooled to room temperature. The crude reaction mixture was washed with $Et_2O$ (2 portions of 15 mL) and then acidified with aqueous 3 M HCl solution to pH ~ 1. The resulting aqueous layer was extracted with EtOAc (3 portions of 25 mL) and the combined organic layers washed with $H_2O$ (25 mL), brine (25 mL), dried ($MgSO_4$) and concentrated to afford crude angelic acid (7.5 g, 90%) as a brown solid that was used in the next step without purification. To a stirred solution of the crude acid (7.5 g, 74 mmol) in MeOH (23 mL) was added solid KOH (4.2 g, 74 mmol) at 0 $^{o}$C. After stirring for ½ h at 0 $^{o}$C, the reaction mixture was concentrated and the crude residue azeotroped with acetone (2 portions of 50 mL), then dried under vacuum over $P_2O_5$ for 48 h. To a suspension of the resulting potassium salt in $Et_2O$ (150 mL) at 0 $^{o}$C was added oxalyl chloride (50 g, 394 mmol), followed by DMF (0.1 mL). The reaction mixture was stirred for 4 h at 0 $^{o}$C, then filtered and concentrated. The residue was rediluted with $CH_2Cl_2$ (100 mL) and then concentrated to dryness (this procedure was repeated 3 times) affording the crude acid chloride which was used without further purification. Following GP 2, *Z*-(**3.13**) was obtained as a white solid (930 mg, 85%); mp 33.0-33.5 $^{o}$C; $^{1}$H-NMR ($C_6D_6$) δ 0.79 (t, 3H, *J* = 7.5 Hz), 1.45 (d, 3H, *J* = 7.0 Hz), 1.95 (q, 2H, *J* = 7.5 Hz), 5.04 (s, 2H), 5.38 (brs, 1H), 5.72 (q, 1H, *J* = 7.0 Hz), 7.00-7.30 (m, 5H); $^{13}$C-NMR ($C_6D_6$) δ 11.9, 12.4, 22.7, 66.5, 128.2, 128.6, 128.6, 136.2, 137.3; IR (neat) 3322, 3064, 3033, 2969, 2935, 2877, 1706, 1523, 1455, 1380, 1351, 1307, 1234, 1097,

1029, 998, 831, 738 $cm^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{13}H_{18}NO_2$ $[M+H]^+$, 220.1338. Found 220.1347.




**(*E*)-(1-Ethyl-propenyl)-carbamic acid benzyl ester (3.13)**

To a solution of *Z*-**3.13** (237 mg, 1.08 mmol) in THF (12 mL) was added KO$^t$Bu (145.5 mg, 1,29 mmol) at room temperature. After stirring for 14 h, the reaction was quenched by the addition of a saturated aqueous $NH_4Cl$ solution (10 mL) at room temperature and extracted with $Et_2O$ (2 portions of 10 mL).The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and concentrated under vacuum. The crude product obtained was purified by column chromatography on silica gel to deliver an approx. 1:1 mixture of geometric isomers (184 mg, 78%). These could be separated by careful preparative thin layer chromatography (toluene:$Et_2O$, 10:1). *E*-(**3.13**) was obtained as a white solid (85 mg, 36%); mp 53.0-54.0 $^oC$; $^1$H-NMR ($C_6D_6$) δ 0.95 (t, 3H, *J* = 7.5 Hz), 1.28 (d, 3H, *J* = 6.8 Hz), 2.34 (brq, 2H, *J* = 7.5 Hz), 4.70 (q, 1H, *J* = 6.8 Hz), 5.05 (s, 2H), 5.50 (brs, 1H), 5.72, 7.00-7.26 (m, 5H); $^{13}$C-NMR ($C_6D_6$) δ 11.7, 12.6, 27.9, 66.7, 110.5, 128.2, 128.5, 128.6, 137.2, 137.3; IR (neat) 3305, 2967, 2751, 1693, 1515, 1450, 1321, 1257, 1108, 966, 848, 738, 698 $cm^{-1}$; HRMS (FAB); Exact mass calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$, 220.1338. Found 220.1348.




**Cyclohex-1-enyl-carbamic acid benzyl ester (3.14)**

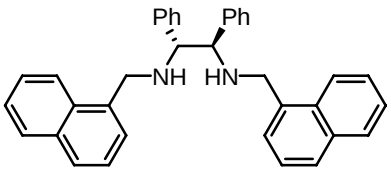
Obtained in 68%; mp 49.0-50.0 $^oC$; $^1$H-NMR ($C_6D_6$) δ 1.26-1.45 (m, 4H), 1.70-1.80 (m, 2H), 1.86-1.98 (m, 2H), 5.03 (s, 2H), 5.31 (brs, 1H), 6.01 (brs, 1H), 7.00-7.25 (m, 5H); $^{13}$C-NMR ($C_6D_6$) δ 22.4, 22.8, 24.1, 27.7, 66.4, 109.3, 128.2, 128.6, 128.6, 132.3, 137.3, 153.2; IR (neat) 3322, 3058, 3033, 2931, 2838, 1706, 1538, 1452, 1380, 1348, 1305, 1232, 1062, 1037, 917, 840, 804, 736, 696 $cm^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{14}H_{18}NO_2$ $[M+H]^+$, 232.1338. Found 232.1342.

**General Procedure for the Preparation of Diamine Ligands (GP 3):**[6.3]

To a solution of (*R*,*R*)-diphenylethylene diamine (0.53 g, 2.5 mmol) in $CH_2Cl_2$ (20 mL) was added $Et_3N$ (0.7 mL, 5.0 mmol) at 0 $^oC$. The substituted benzoly chloride (5.0 mmol) was added dropwise to the reaction mixture at 0 $^oC$. A heavy suspension

[6.3] Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507 and references therein.

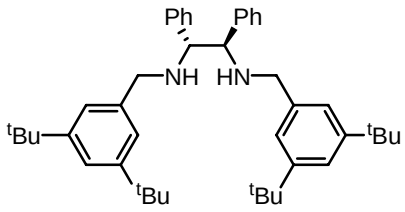
was obtained during the addition. After 1 h at ice bath temperature, the reaction mixture was allowed to warm to room temperature and stirred for further 5 h. The reaction was quenched by addition of 10% aqueous HCl (5 mL) and the mixture was extracted with $CH_2Cl_2$ (2 portions of 10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 portions of 15 mL), brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated to afford (*R*,*R*)-*N*,*N'*-dibenzoyl 1,2-diphenyletylene diamine in quantitative yield. In some cases the *N*,*N'*-diacyl diamine was insoluble in organic solvents. In such cases, a simple filtration of the reaction mixture followed by washing with water afforded the almost pure desired compound. The solid was dried effectively by azeotropic distillation with benzene. To a solution of the dried *N*,*N'*-diacyl diamine (1.2 mmol) in THF (5 mL) was added $BH_3$·THF (1.0 M, 30 eq.) at 0 $^oC$. The reaction mixture was refluxed for 10-20 h and cooled to room temperature. The reaction was quenched by careful addition of MeOH (4 mL) at 0 $^oC$ and the mixture was concentrated. MeOH (4 mL) and conc. HCl (10 mL) were added to the residue at ice bath temperature and the resulting mixture was refluxed for 2 h. The reaction mixture was alkalized with 10% aqueous NaOH and extracted with $CH_2Cl_2$ (3 portions of 15 mL). The organic layer was washed with brine (20 mL) and dried ($K_2CO_3$). The solvent was evaporated and the residue was purified by chromatography or recrystallization to afford the diamine ligand in moderate to high yield.




**(1*R*,2*R*)-*N*,*N'*-Bis-naphthalen-1-ylmethyl-1,2-diphenyl-ethane-1,2-diamine (1.a)**

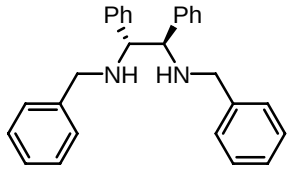
This compound was best prepared according to the following procedure: To a suspension of (*R*,*R*)-1,2-diphenylethylnene diamine (900 mg, 4.24 mmol) and $K_2CO_3$ (2.34 g, 16.9 mmol) in DMF (5 mL) was added a solution of 1-(chloromethyl)naphthalene (1.5 g, 8.46 mmol) in DMF (7 mL). The reaction mixture was stirred for 2 days at room temperature, after which it was quenched by addition of water (5 mL) and the mixture extracted with EtOAc (2 portions of 8 mL). The organic layers were washed several times with water, followed by brine (10 mL). The organic layer was dried ($K_2CO_3$), the solvent was evaporated and the residue was purified by column chromatography on silica gel to afford (**1.a**) as a colourless solid (1,2 g, 53%); mp 52.0-53.0 $^oC$; $^1$H-NMR ($CDCl_3$) δ 2.49 (brs, 2H), 3.78 (s, 2H), 3.89 (d, 2H, *J* = 13.0 Hz), 4.03 (d, 2H, *J* = 13.0 Hz), 7.05-7.50 (m, 18H), 7.73 (d, 2H, *J* = 8.1Hz), 7.82 (d, 2H, *J* = 8.3 Hz), 7.92 (d, 2H, *J* = 8.6 Hz); $^{13}$C-NMR ($CDCl_3$) δ 49.5, 69.1, 124.0, 125.2, 125.5, 125.8, 126.1, 127.0, 127.6, 128.0, 128.5, 131.9, 133.8, 136.1, 141.3; IR (KBr) 3310, 3053, 3033, 2911,

2840, 1594, 1504, 1455, 1262, 1111, 1073, 1021, 858, 780, 699, 565 $cm^{-1}$; LRMS (EI) *m/z* = 492 $[M]^{2+}$; Anal. Calcd for $C_{36}H_{32}N_2$: C, 87.77, H, 6.55, N, 5.69. Found: C, 85.57; H, 6.83; N, 5.67; $[\alpha]_D^{24}$ +2.2 (*c* 0.99, $CHCl_3$).




**(1*R*,2*R*)-*N*,*N*'-Bis(3,5-di-*tert*-butyl-benzyl)-1,2-diphenyl-ethane-1,2-diamine (3.b)**

Obtained in 48%; mp 115.0-117.0 °C; $^1$H-NMR ($CDCl_3$) δ 2.18 (s, 36H), 3.49 (d, 2H, *J* = 12.8 Hz), 3.62 (d, 2H, *J* = 12.8 Hz), 3.73 (s, 2H), 6.90-7.40 (m, 18H); $^{13}$C-NMR ($CDCl_3$) δ 31.5, 34.7, 52.0, 68.3, 77.2, 120.8, 122.4, 126.9, 127.9, 128.1, 139.4, 141.5, 150.6; IR (KBr) 2963, 2903, 2866, 1599, 1475, 1455, 1362, 712, 699 $cm^{-1}$; LRMS (EI) *m/z* = 308 $[M]^{2+}$; Anal. Calcd. for $C_{44}H_{60}N_2$: C, 85.66, H, 9.80, N, 4.54. Found: C, 85.70; H, 9.90; N, 4.52; $[\alpha]_D^{24}$ -10.3 (*c* 0.55, $CHCl_3$).



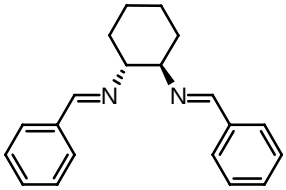

**(1*R*,2*R*)-*N*,*N*'-dibenzyl-1,2-diphenyl-ethane-1,2-diamine (3.d)**

Obtained in 67%; mp 64.0-65.2 °C; $^1$H-NMR ($CDCl_3$) δ 2.18 (brs), 3.42 (d, 2H, *J* = 13.3 Hz), 3.59 (d, 2H, *J* = 13.3 Hz), 3.64 (s, 2H), 6.80-7.45 (m, 20H); $^{13}$C-NMR ($CDCl_3$) δ 51.3, 68.3, 126.8, 126.9, 128.0, 128.0, 128.1, 128.3, 140.5, 141.1; IR (KBr) 3310, 3085, 3062, 2830, 1494, 1112, 739, 697 $cm^{-1}$; LRMS (EI) *m/z* = 196 $[M]^{2+}$; Anal. Calcd. for $C_{28}H_{28}N_2$: C, 85.67, H, 7.19, N, 7.14. Found: C, 85.94; H, 7.35; N, 7.12; $[\alpha]_D^{24}$ -27.9 (*c* 1.0, $CHCl_3$).

**General Procedure for the Preparation of Diimine Ligands (GP 4):**[6.4]

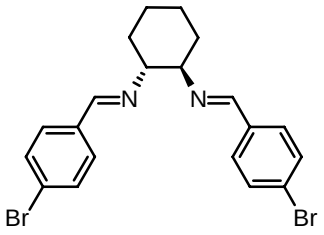
The aldehyde (neat, 2.0 eq.) is added to a 0.2 M solution of (*R*,*R*)-1,2-cyclohexyldiamine (1.0 eq) in EtOH. This mixture was heated to reflux for 1-2 h, after which $H_2O$ was added dropwise to the resulting solution at 0 °C (occasionally the product begins to crystallize upon cooling prior to addition of water). The resulting crystalline solid was collected by filtration and washed with a small portion of abs. EtOH.

[6.4] Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2297.



**(1*R*,2*R*)-(*N*$^1$-*E*,*N*$^2$-*E*)-*N*$^1$,*N*$^2$-Dibenzylidenecyclohexane-1,2-diamine** (**3.j**)

Obtained in 85%; mp 99.0-100.2 $^{o}$C; $^{1}$H-NMR ($CDCl_3$) δ 1.50 (m, 2H), 1.86 (s, 6H), 3.42 (m, 2H), 7.29 (m, 2H), 7.33 (d, 4H, *J* = 2.2 Hz), 7.59 (d, 4H, *J* = 2.2 Hz), 8.21 (s, 2H); $^{13}$C-NMR ($CDCl_3$) δ 24.46, 32.93, 73.76, 127.87, 128.32, 130.16, 136.33, 160.94; LRMS (FAB+) *m/z* = 291 $[M+H]^+$; $[\alpha]_D^{24}$ -202.0 (*c* 0.5, $CHCl_3$).



**(1*R*,2*R*)-(*N*$^1$-*E*,*N*$^2$-*E*)-*N*$^1$,*N*$^2$-bis-(4-bromo-benzylidene)cyclohexane-1,2-diamine** (**3.u**)

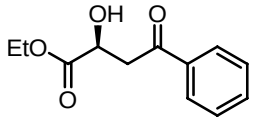
Obtained in 91%; mp 124.3-125.5 $^{o}$C; $^{1}$H-NMR ($CDCl_3$) δ 1.49 (m, 2H), 1.86 (s, 6H), 3.38 (m, 2H), 7.44 (s, 8H), 8.11 (s, 2H); $^{13}$C-NMR ($CDCl_3$) δ 24.42, 32.81, 73.77, 124.69, 129.32, 131.67, 135.15, 159.74; LRMS (FAB+) *m/z* = 499 $[M+H]^+$; $[\alpha]_D^{24}$ -266.0 (*c* 1.2, $CHCl_3$).

## 6.3 - Compounds from addition reactions

**Procedure to obtained monomeric ethyl glyoxylate:**
Polymeric ethyl glyoxylate (as a toluene solution) (30 g) was concentrated under vacuum (<1mmHg) at room temperature to completely remove the toluene. To the residue obtained was added $P_2O_5$ (*ca.* 300 mg) and this mixture was distilled at reduced pressure (150 mmHg, 80 $^{o}$C), delivering monomeric ethyl glyoxylate as a pale yellow liquid.
Note: The freshly distilled monomeric ethyl glyoxylate begins to polymerize within less than 30 min. into a viscous liquid and therefore it should be used immediately after distillation.

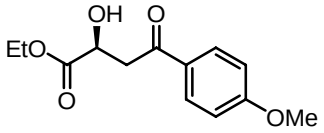
**General procedure for the catalysed reactions of enecarbamates with ethyl glyoxylate followed by acidic hydrolysis (GP 5):**
Metal salts (0.020 mmol, 10 mol%) were weighed in a dry-box into a dried two neck flask fitted with a 3-way tap. The ligand (best results obtained with diimine (**3.u**)) (0.022 mmol, 11 mol%) was added under a flow of argon, the flask sealed and evacuated-back-filled with argon (3 cycles). The specified solvent (typically $CH_2Cl_2$)

(1.5 mL) was added *via* syringe and the mixture obtained was stirred at room temperature over *ca.* 12 h under an argon atmosphere to ensure complete formation of the L.A.-ligand complex. After being cooled to the wanted temperature (usually 0 $^{o}$C), a solution of freshly distilled ethyl glyoxylate (0.24 mmol, 1.2 eq.) in the specified solvent (typically $CH_2Cl_2$) (0.8 mL) and a solution of the enecarbamate (0.2 mmol, 1.0 eq) in the specified solvent (typically $CH_2Cl_2$) (0.8 mL) were added sequentially in one portion. After stirring at that temperature for the stated time (usually 1 h), the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1.5 mL) and then stirred at room temperature (exposed to air) for approx. 1-2 min. The reaction mixture was transferred to a separating funnel and extracted with $CH_2Cl_2$ (3 portion of 2 mL). The organic layers were combined, washed with brine (3 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue thus obtained was dissolved in EtOH (3 mL), cooled to 0 $^{o}$C and hydrolyzed with a 48% HBr aqueous solution (0.3 mL). The reaction mixture was stirred at room temperature for approx. 1½ min., after which it was cooled to 0 $^{o}$C and quenched with saturated aqueous $NaHCO_3$ (10 mL). The reaction mixture was transferred to a separating funnel and extracted with $CH_2Cl_2$ (3 portions of 5 mL)).The organic layers were combined, washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was loaded onto preparative TLC plates with $CH_2Cl_2$ and purified by eluting with benzene:acetone, 5:1.



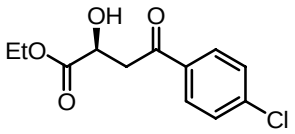

**(2*S*)-2-Hydroxy-4-oxo-4-phenyl-butyric acid ethyl ester (4.14)**

Obtained in 93% and 97% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.27 (t, 3H, *J* = 7.1 Hz), 3.29 (brs, 1H), 3.44 (dd, 1H, *J* = 6.1, 17.6 Hz), 3.52 (dd, 1H, *J* = 3.9, 17.6 Hz), 4.25 (q, 2H, *J* = 7.1 Hz), 4.61-4.67 (m, 1H), 7.44-7.50 (m, 2H), 7.54-7.60 (m, 1H), 7.92-7.98 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 14.0, 42.1, 61.8, 67.1, 128.1, 128.6, 133.5, 136.4, 173.7, 197.5; IR (neat) 3475, 3063, 2983, 1737, 1687, 1597, 1580, 1449, 1368, 1213, 1098, 1045, 860, 759, 690, 582, 499 cm$^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{12}H_{15}O_4$ $[M+H]^+$, 223.0970. Found 223.0972; HPLC, Daicel Chiralcel ADH, hexane:$^{i}$PrOH 4:1, flow rate = 0.5 mLmin$^{-1}$: *tr* = 19.9 min (*S*), *tr* = 22.2 min (*R*).



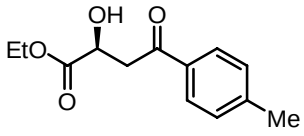

**(2*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-4-oxo-butyric acid ethyl ester (4.17)**

Obtained in 94% and 93% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.1 Hz), 3.41 (dd, 1H, *J* = 5.9, 17.4 Hz), 3.48 (dd, 1H, J = 4.0, 17.4 Hz), 3.48 (brd, 1H, *J* = 6.8 Hz), 3.87 (s, 3H), 4.26 (q, 2H, *J* = 7.1 Hz), 4.60-4.70 (m, 1H), 6.91-6.97 (m, 2H), 7.90-7.97 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 14.0, 41.7, 55.4, 61.7, 67.3, 113.8, 129.5, 130.4, 163.8, 173.8, 196.1; IR (neat) 3483, 2979, 2841, 1739, 1677, 1600, 1575, 1512, 1421, 1368, 1265, 1172, 1099, 1027, 988, 895, 834, 737, 579 $cm^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{13}H_{17}O_5$ $[M+H]^+$, 253.1076. Found 253.1097; HPLC, Daicel Chiralcel ADH, hexane:$^{i}$PrOH = 4:1, flow rate = 0.4 $mLmin^{-1}$: *tr* = 43.1 min (*S*), *tr* = 45.7 min (*R*).



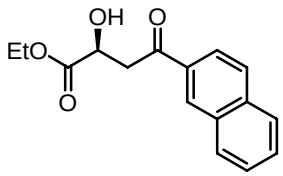

**(2*S*)-4-(4-Chloro-phenyl)-2-hydroxy-4-oxo-butyric acid ethyl ester (4.18)**

Obtained in 97% and 97% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.1 Hz), 3.42 (dd, 1H, *J* = 6.1, 17.3 Hz), 3.49 (dd, 1H, J = 3.9, 17.3 Hz), 3.41-3.47 (brd, 1H), 3.87 (s, 3H), 4.26 (q, 2H, *J* = 7.1 Hz), 4.62-4.70 (m, 1H), 7.42-7.48 (m, 2H), 7.86-7.93 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 14.1, 42.2, 62.0, 67.1, 129.0, 129.6, 134.8, 140.1, 173.7, 196.3; IR (neat) 3480, 2982, 1739, 1684, 1590, 1573, 1402, 1213, 1093, 1045, 820, 531 $cm^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{12}H_{14}ClO_4$ $[M+H]^+$, 257.0580. Found 257.0584; HPLC, Daicel Chiralcel ADH, hexane:$^{i}$PrOH = 4:1, flow rate = 0.5 $mLmin^{-1}$: *tr* = 24.2 min (*S*), *tr* = 26.5 min (*R*).



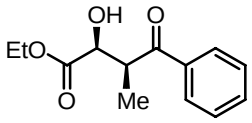

**(2*S*)-2-Hydroxy-4-oxo-4-*p*-tolyl-butyric acid ethyl ester (4.19)**

Obtained in quantitative yield and 96% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.1 Hz), 2.41 (s, 3H), 3.44 (dd, 1H, *J* = 5.9, 17.4 Hz), 3.51 (dd, 1H, *J* = 4.0, 17.4 Hz), 3.45-3.55 (brd, 1H), 4.26 (q, 2H, *J* = 7.1 Hz), 4.66 (dt, 1H, *J* = 4.2, 5.5 Hz), 7.26 (appd, 2H, *J* = 8.0 Hz), 7.85 (appd, 2H, *J* = 8.2 Hz); $^{13}$C-NMR ($CDCl_3$) δ 14.0, 21.6, 42.0, 61.7, 67.2, 128.2, 129.3, 133.9, 144.4, 173.7, 197.1; IR (neat) 3483, 2981, 1742, 1682, 1606, 1405, 1365, 1212, 1098, 1044, 813, 578 $cm^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1120; HPLC, Daicel Chiralcel ADH, hexane:$^{i}$PrOH = 4:1, flow rate = 0.3 $mLmin^{-1}$: *tr* = 36.1 min (*S*), *tr* = 38.1 min (*R*).



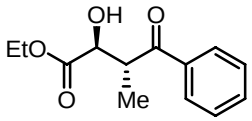
**(2*S*)-2-Hydroxy-4-naphthalen-2-yl-4-oxo-butyric acid ethyl ester (4.20)**

Obtained in 91% and 96% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.1 Hz), 3.52 (d, 1H, *J* = 5.9 Hz), 3.59 (dd, 1H, *J* = 6.1, 17.3 Hz), 3.66 (dd, 1H, *J* = 3.9 , 17.3 Hz), 4.28 (q, 2H, *J*= 7.1 Hz), 4.73 (dt, 1H , J = 4.2, 5.4 Hz), 7.50-7.65 (m, 2H), 7.82-8.20 (m, 4H), 8.45 (s, 1H); $^{13}$C-NMR ($CDCl_3$) δ 14.1, 42.3, 61.9, 67.3, 123.6, 126.9, 127.8, 128.6, 128.8, 129.6, 130.2, 132.4, 133.8, 135.8, 173.9, 197.5; IR (neat) 3481, 3058, 2982, 1741, 1681, 1627, 1469, 1369, 1209, 1097, 1045, 859, 824, 749, 477 $cm^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{16}H_{17}O_4$ $[M+H]^+$, 273.1127. Found 273.1125; HPLC, Daicel Chiralcel ADH, hexane:$^{i}$PrOH = 4:1, flow rate = 0.5 $mLmin^{-1}$: *tr* = 27.0 min (*S*), *tr* = 30.4 min (*R*).



**(2*S*,2*S*)-2-Hydroxy-3-methyl-4-oxo-4-phenyl-butyric acid ethyl ester (4.21)**

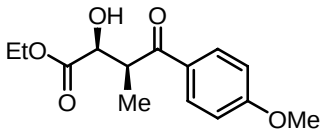
Obtained in 96% and 98% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.26 (t, 3H, *J* = 7.0 Hz), 1.29 (d, 3H, *J* = 7.0 Hz), 3.28 (brs, 1H), 3.93 (dq, 1H, *J* = 4.2, 7.0 Hz), 4.25 (q, 2H, *J* = 7.0 Hz), 4.58 (d, 1H, *J* = 4.2 Hz), 7.40-7.65 (m, 3H), 7.90-8.05 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 12.1, 14.0, 44.3, 61.9, 71.6, 128.4, 128.7, 133.3, 135.7, 173.1, 201.6; IR (neat) 3480, 3063, 2978, 2936, 1734, 1678, 1596, 1579, 1449, 1369, 1217, 1133, 1062, 1023, 1001, 975, 952, 862, 794, 708 $cm^{-1}$.



**(2*S*,3*R*)-2-Hydroxy-3-methyl-4-oxo-4-phenyl-butyric acid ethyl ester (4.21)**

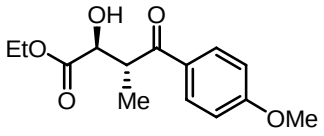
Obtained in 95% and 98% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.20 (t, 3H, *J* = 7.1 Hz), 1.36 (d, 3H, *J* = 7.3 Hz), 3.61 (d, 1H, *J* = 8.3 Hz), 3.98 (dq, 1H, *J* = 4.6, 7.1 Hz), 4.10-4.25 (m, 2H);, 4.39 (dd, 1H, *J* = 4.6, 8.3 Hz), 7.40-7.65 (m, 3H); $^{13}$C-NMR ($CDCl_3$) δ 14.0, 14.1, 44.0, 61.5, 73.1, 128.3, 128.7, 133.4, 135.9, 173.1; IR (neat) 3481, 3059, 2981, 2941, 1738, 1685, 1588, 1454, 1372, 1255, 1209, 1144, 1092, 1024, 973, 701 $cm^{-1}$.

HRMS (FAB); Exact mass calcd for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1118; HPLC, Daicel Chiralcel AS+ADH+AD, hexane:$^{i}$PrOH = 4:1, flow rate = 0.5 $mLmin^{-1}$: *tr* = 46.7 min (2*S*,3*S*), *tr* = 50.6 min (2*R*,3*R*), *t*r = 54.3 min (2*S*,3*R*), *tr* = 61.9 min (2*R*,3*S*).




**(2*S*,3*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-3-methyl-4-oxo-butyric acid ethyl ester (4.22)**

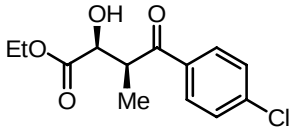
Obtained in 97% and 98% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.1 Hz), 1.29 (d, 3H, *J* = 7.1 Hz), 3.35 (brs, 1H), 3.84-3.96 (m, 4H), 4.27 (q, 2H, *J* = 7.1 Hz), 4.58 (d, 1H, *J* = 4.2 Hz), 6.96 (appd, 2H, *J* = 9.0 Hz), 7.30-7.45 (m, 5H), 7.95 (appd, 2H, *J* = 8.8 Hz); $^{13}$C-NMR ($CDCl_3$) δ 12.3, 14.0, 43.7, 55.4, 61.8, 71.7, 113.9, 128.5, 130.7, 163.7, 173.1, 200.4; IR (neat) 3477, 2979, 2935, 2850, 1730, 1670, 1600, 1573, 1510, 1463, 1420, 1308, 1261, 1173, 1125, 1027, 976, 843, 770, 604 cm$^{-1}$.




**(2*S*,3*R*)-2-Hydroxy-4-(4-methoxy-phenyl)-3-methyl-4-oxo-butyric acid ethyl ester (4.22)**

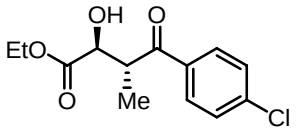
Obtained in 96% and 98% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.19 (t, 3H, *J* = 7.1 Hz), 1.36 (d, 3H, *J* = 7.3 Hz), 3.75 (d, 1H, *J* = 9.3 Hz), 3.88 (s, 3H), 3.94 (dq, 1H, *J* = 4.6, 7.3 Hz), 4.15 (appdq, 2H, *J* = 3.2, 7.1 Hz), 4.36 (dd, 1H, *J* = 4.6, 9.3 Hz), 6.92-6.99 (m, 2H), 7.90-7.97 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 14.0, 14.6, 43.2, 55.5, 61.4, 73.4, 113.9, 128.7, 130.8, 163.8, 173.2, 201.9; IR (neat) 3478, 2979, 2941, 2843, 1738, 1671, 1599, 1580, 1510, 1457, 1419, 1370, 1308, 1257, 1216, 1172, 1092, 1026, 974, 841 cm$^{-1}$.

HRMS (FAB); Exact mass calcd for $C_{14}H_{19}O_5$ $[M+H]^+$, 267.1232. Found 267.1232; HPLC, Daicel Chiralcel ADH, hexane:$^{i}$PrOH = 4:1, flow rate = 0.2 mLmin$^{-1}$: *tr* = 60.5 min (2*R*,3*R*), *tr* = 65.4 min (2*S*,*3S*), *tr* = 75.2 min (2*R*,3*S*), *tr* = 78.9 min (2*S*,3*R*).




**(2*S*,3*S*)-4-(4-Chloro-phenyl)-2-hydroxy-3-methyl-4-oxo-butyric acid ethyl ester (4.23)**

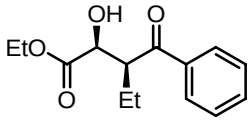
Obtained in 79% and 98% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.26 (t, 3H, *J* = 7.0 Hz), 1.28 (d, 3H, *J* = 7.0 Hz), 3.27 (brs, 1H), 3.87 (dq, 1H, *J* = 4.4, 7.0 Hz), 4.25 (q, 2H, *J* = 7.0 Hz), 4.55 (d, 1H, *J* = 4.4 Hz), 7.40-7.55 (m, 2H), 7.84-7.97 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 12.1, 14.0, 44.4, 62.0, 71.5, 129.0, 129.8, 134.1, 139.7, 173.1, 200.3; IR (neat) 3485, 2982, 2938, 1730, 1682, 1589, 1571, 1488, 1455, 1401, 1217, 1132, 1092, 1013, 977, 843, 758, 692, 533, 478 cm$^{-1}$.




**(2*S*,3*R*)-4-(4-Chloro-phenyl)-2-hydroxy-3-methyl-4-oxo-butyric acid ethyl ester (4.23)**

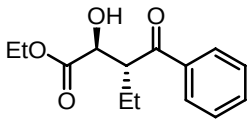
Obtained in 85% and 98% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.21 (t, 3H, *J* = 7.1 Hz), 1.34 (d, 3H, *J* = 7.1 Hz), 3.53 (d, 1H, *J* = 8.2 Hz), 3.91 (dq, 1H, *J* = 5.0, 7.1 Hz), 4.08-4.24 (m, 2H), 4.38 (dd, 1H, *J* = 5.0, 8.2 Hz), 7.42-7.52 (m, 2H), 7.80-7.95 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 13.9, 14.0, 44.1, 61.6, 73.0, 129.0, 129.8, 134.3, 139.9, 173.0, 201.8; IR (neat) 3478, 3092, 2982, 2935, 1738, 1686, 1589, 1455, 1402, 1255, 1208, 1144, 1092, 1022, 976, 842, 751, 527 cm$^{-1}$.

HRMS (FAB); Exact mass calcd for $C_{13}H_{16}ClO_4$ $[M+H]^+$, 271.0737. Found 271.0745; HPLC, Daicel Chiralcel AS, hexane:$^{i}$PrOH = 4:1, flow rate = 0.5 mLmin$^{-1}$: *tr* = 15.1 min (2*S*,3*S*), *tr* = 16.6 min (2*S*,3*R*), *tr* = 21.4 min (2*R*,3*S*), *tr* = 23.9 min (2*R*,3*R*).




**(2*S*,3*S*)-3-Benzoyl-2-hydroxy-pentanoic acid ethyl ester (4.26)**

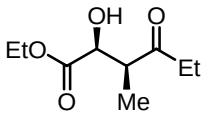
Obtained in 92% and 98% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 0.93 (t, 3H, *J* = 7.5 Hz), 1.19 (t, 3H, *J* = 7.1 Hz), 1.70-2.05 (m, 2H), 3.18 (brs, 1H), 3.83 (dt, 1H, *J* = 5.3, 8.3 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 4.51, (d, 1H, *J* = 5.3 Hz), 7.42-7.54 (m, 2H), 7.54-7.62 (m, 1H), 7.90-8.02 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 12.0, 13.9, 21.3, 51.2, 61.9, 71.1, 128.3, 128.6, 133.2, 137.0, 173.6, 201.5; IR (neat) 3477, 2972, 2876, 1738, 1675, 1596, 1447, 1372, 1255, 1220, 1118, 1023, 931, 849, 779, 701 cm$^{-1}$.




**(2*S*,3*R*)-3-Benzoyl-2-hydroxy-pentanoic acid ethyl ester (4.26)**

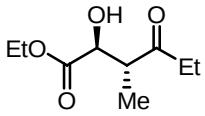
Obtained in 58% and 98% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.04 (t, 3H, *J* = 7.6 Hz), 1.15 (t, 3H, *J* = 7.1 Hz), 1.80-1.95 (m, 2H),3.70 (d, 1H, *J* = 9.5 Hz), 3.83 (dt, 1H, *J* = 4.2, 7.1 Hz), 4.09 (q, 2H, *J* = 7.1 Hz), 4.43 (dd, 1H, *J* = 4.2, 9.5 Hz), 7.46-7.52 (m, 2H), 7.56-7.63 (m, 1H), 7.88-7.95 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 12.0, 13.9, 22.3, 50.1, 61.4, 71.3, 128.3, 128.7, 133.5, 136.6, 173.4, 203.9; IR (neat) 3485, 3062, 2966, 2941, 2875, 1738, 1682, 1596, 1579, 1448, 1368, 1268, 1208, 1134, 1100, 1028, 914, 849, 785, 699 cm$^{-1}$.

HRMS (FAB); Exact mass calcd for $C_{14}H_{19}O_4$ $[M+H]^+$, 251.1283. Found 251.1277; HPLC, Daicel Chiralcel AS, hexane:$^{i}$PrOH = 4:1, flow rate = 0.5 mLmin$^{-1}$: *tr* = 13.7 min (2*S*,3*S*), *tr* = 15.3 min (2*S*,3*R*), *t*r = 17.6 min (2*R*,3*R*), *tr* = 23.1 min (2*R*,3*S*).




**(2*S*,3*S*)-2-Hydroxy-3-methyl-4-oxo-hexanoic acid ethyl ester (4.27)**

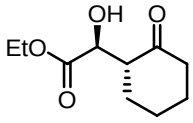
Obtained in 89% and 98% *ee*; $^{1}$H-NMR ($C_6D_6$) δ 0.89 (t, 3H, *J* = 7.1 Hz), 0.99 (d, 3H, *J* = 7.2 Hz), 1.97-2.08 (m, 2H), 2.70 (dq, 1H, *J* = 4.9, 7.2 Hz), 3.39 (d, 1H, *J* = 6.7 Hz), 3.80-4.00 (m, 2H), 4.11 (dd, 1H, *J* = 4.9, 6.7 Hz); $^{13}$C-NMR ($CDCl_3$) δ 7.58, 12.8, 14.0, 34.6, 49.4, 61.3, 73.0, 173.5, 211.3; IR (neat) 3484, 2981, 2940, 1739, 1716, 1459, 1409, 1375, 1268, 1209, 1108, 1066, 1025, 975, 862, 808, 748 cm$^{-1}$.




**(2*S*,3*R*)-2-Hydroxy-3-methyl-4-oxo-hexanoic acid ethyl ester (4.27)**

Obtained in 83% and 97% *ee*; $^{1}$H-NMR ($C_6D_6$) δ 0.87 (t, 3H, *J* = 7.1 Hz), 0.93 (t, 3H, *J* = 7.3 Hz), 1.02 (d, 3H, *J* = 7.2 Hz), 1.95-2.22 (m, 2H), 2.65 (dq, 1H, *J* = 4.4, 7.2 Hz), 3.05-3.23 (m, 1H), 3.80-4.00 (m, 2H), 4.38-4.47 (m, 1H); $^{13}$C-NMR ($C_6D_6$) δ 7.7, 11.0, 14.0, 34.0, 49.5, 61.6, 71.7, 173.7, 209.9; IR (neat) 2981, 2940, 1733, 1716, 1459, 1373, 1218, 1145, 1025, 977, 862, 800, 752 cm$^{-1}$.

HRMS (FAB); Exact mass calcd for $C_9H_{17}O_4$ $[M+H]^+$, 189.1127. Found 189.1120.



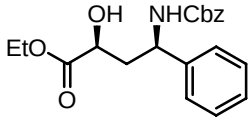

**(1*S*,2*R*)-Hydroxy-(2-oxo-cyclohexyl)-acetic acid ethyl ester (4.28)**

Obtained in 85% and 94% *ee*; $^{1}$H-NMR ((1*S*,1'*R*), tentative assignment) ($C_6D_6$) δ 0.95 (t, 3H, *J* = 7.1 Hz), 0.94-1.20 (m, 2H), 1.30-1.42 (m, 2H), 1.56-1.84 (m, 3H), 2.02-2.12 (m, 1H), 2.60-2.70 (m, 1H), 3.35 (d, 1H, *J* = 7.2 Hz), 3.84 (dd, 1H, *J* = 3.2, 7.2 Hz), 4.02 (dq, 2H, *J* = 1.9, 7.1 Hz); $^{13}$C-NMR ($CDCl_3$) δ 14.1, 24.8, 26.9, 30.1, 42.0, 53.7, 61.6, 71.1, 173.4, 211.2.

$^{1}$H-NMR distinguishable *syn* peaks ($C_6D_6$) δ 0.88 (t, 3H, *J* = 7.1 Hz), 2.12-2.21 (m, 1H), 2.48-2.57 (m, 1H), 2.94 (d, 1H, *J* = 5.0 Hz), 4.60 (dd, 1H, *J* = 3.2, 5.0 Hz); $^{13}$C-NMR distinguishable *syn* peaks ($CDCl_3$) δ 14.2, 24.6, 27.1, 41.9, 53.8, 61.7, 69.2, 173.6, 210.4.

HRMS (FAB); Exact mass calcd for $C_{10}H_{17}O_4$ $[M+H]^+$, 201.1127. Found 201.1127.

**Example of a procedure for the catalysed reaction of enecarbamates with ethyl glyoxylate followed by reduction:**



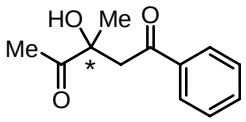

**(2*S*,4*R*)-4-Benzyloxycarbonlyamino-2-hydroxy-4-phenyl-butyric acid ethyl ester (4.31)**

A solution of ligand (**3.u**) (9.9 mg, 0.022 mmol) in $CH_2Cl_2$ (1.5 mL) was added to $CuClO_4 \cdot 4CH_3CN$ (6.5 mg, 0.020 mmol) under argon. The yellow solution obtained was stirred at room tempearture over 8 h and cooled to 0 $^oC$. Freshly distilled ethyl gyloxylate (100 μL, 0.40 mmol) in $CH_2Cl_2$ (0.8 mL) was added followed by a solution of enecarbamate (**1.37**) in $CH_2Cl_2$ (0.8 mL) in one portion. The reaction mixture was stirred at 0 $^oC$ for 1 h and then quenched by addition of saturated aqueous $NaHCO_3$ (1.5 mL). After reaching room temperature, the mixture transferred into an extracting funnel and extracted with $CH_2Cl_2$ (3 portions of 2 mL). The organic layer was washed with brine (3 mL), dried ($MgSO_4$) and the solvent removed under vacuum. The residue thus obtained was taken in benzene and concentrated under vacuum (three times) to remove the last traces of water. THF (2.0 mL) and MeOH (0.5 mL) were added to the residue and this solution was cooled to -78 $^oC$. Diethyl methoxyborane (79μL, 0.6 mmol) was added and the mixture was stirred for 15 min. at this temperature, after which $NaBH_4$ (22.7 mg, 0.6 mmol) was added in one portion. After stirring at -78 $^oC$ for 2 h the reaction was quenched by addition of AcOH (0.3 mL) and was allowed to warm to ice bath temperature. The mixture was alkalized at 0 $^oC$ by addition of saturated aqueous $NaHCO_3$ and extracted with $Et_2O$ (2 portions of 3 mL). The combined organic fractions were washed with brine (3 mL), dried ($MgSO_4$) and then concentrated under vacuum. The crude product obtained was purified by preparative TLC to deliver (**4.31**) (46.5 mg, 65% over two steps, *syn*:*anti* = 94:6). $^1$H-NMR ($CDCl_3$) δ 1.23 (t, 3H × 19/20, $J$ = 7.1 Hz), 1.25 (t, 3H × 1/20, $J$ = 7.0 Hz), 1.95-2.40 (m, 2H), 3.33 (brs, 1H × 19/20), 3.51 (brs, 1H × 1/20), 4.00-4.40 (m, 3H), 4.85-5.20 (m, 3H), 5.52 (d, 1H × 19/20, $J$ = 7.3 Hz), 5.96 (d, 1H × 1/20, $J$ = 8.2 Hz), 7.00-7.60 (m, 10 H); $^{13}$C-NMR ($CDCl_3$) δ 14.1, 40.3, 52.6, 61.8, 66.8, 68.4, 126.4, 127.6, 128.1, 128.4, 128.7, 136.3, 141.4, 155.7, 174.4; LRMS (FAB) m/z = 358 $[M+H]^+$.

$^{13}$C-NMR distinguishable *anti* peaks ($CDCl_3$) δ 40.2, 52.4, 67.8, 126.2, 127.4, 141.1, 156.0, 174.3.

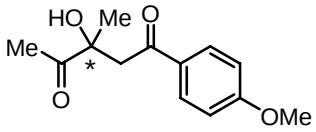
**General procedure for the catalysed reactions of enecarbamates with butane-2,3-dione followed by acidic hydrolysis (GP 6):**

Metal salts (typically $Ni(OTf)_2$ and $Cu(OTf)_2$) (0.020 mmol, 10 mol%) were weighed in a dry-box into a dried two neck flasks fitted with a 3-way tap. Diamine (**3.d**) (0.022 mmol, 11 mol%) was added under a flow of argon, the flask sealed and evacuated-back-filled with argon (3 cycles). $CH_2Cl_2$ (1.5 mL) was added *via* syringe and the mixture obtained was stirred at room temperature over *ca.* 12 h under an argon atmosphere to ensure complete formation of the catalyst. After being cooled to the wanted temperature (usually 0 $^oC$), a solution of butane-2,3-dione (0.40 mmol, 2.0 eq.) in $CH_2Cl_2$ (0.7 mL) and a solution of the enecarbamate (0.2 mmol, 1.0 eq) in $CH_2Cl_2$ (0.7 mL) were added sequentially in one portion. After stirring at that temperature for the stated time (best results were obtained for a 14 days period), the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (1.5 mL) and then stirred at room temperature (exposed to air) for approx. 1-2 min. The reaction mixture was transferred to a separating funnel and extracted with $CH_2Cl_2$ (3 portions of 2 mL). The organic layers were combined, washed with brine (3 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue thus obtained was dissolved in EtOH (3 mL), cooled to 0 $^oC$ and hydrolyzed with a 48% HBr aqueous solution (0.3 mL). The reaction mixture was stirred at room temperature for approx. 1½ min., after which it was cooled to 0 $^oC$ and quenched with saturated aqueous $NaHCO_3$ (10 mL). The reaction mixture was transferred to a separating funnel and extracted with $CH_2Cl_2$ (3 portions of 5 mL). The organic layers were combined, washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was loaded onto preparative TLC plates with $CH_2Cl_2$ and purified by eluting with benzene:acetone, 7:1.



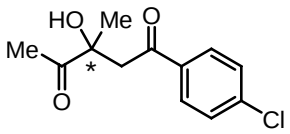

**3-Hydroxy-3-methyl-1-phenylpentane-1,4-dione (4.41)**

Obtained in 94% and 84% *ee*; $^1$H-NMR ($CDCl_3$) δ 1.31 (s, 3H), 2.31 (s, 3H), 3.17 (d, 1H, $J$ = 17.9 Hz), 3.73 (d, 1H, $J$ = 17.2 Hz), 4.30-4.48 (brs, 1H), 7.41 (t, 2H, $J$ = 7.6 Hz), 7.53 (t, 1H, $J$ = 7.6 Hz) 7.87 (d, 2H, $J$ = 8.2 Hz); $^{13}$C-NMR ($CDCl_3$) δ 24.3, 25.2, 47.1, 78.2, 128.3, 128.7, 133.9, 136.1, 200.6, 213.4, ; IR (neat) 3461, 1711, 1675 $cm^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{12}H_{15}O_3$ $[M+H]^+$, 207.1021. Found 207.1029. HPLC, Daicel Chiralcel ADH, hexane:$^i$PrOH = 19:1, flow rate = 0.5 $mLmin^{-1}$: *tr* = 26.9 min (major enantiomer), *tr* = 28.1 min (minor enantiomer).



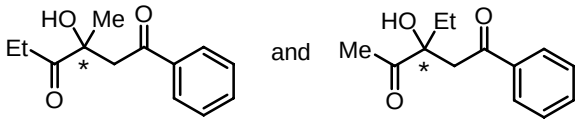
**3-Hydroxy-1-(4-methoxyphenyl)-3-methylpentane-1,4-dione (4.42)**

Obtained in 59% and 65% *ee*; mp 123.0-124.0 $^{o}$C; $^{1}$H-NMR ($CDCl_3$) δ 1.29 (s, 3H), 2.31, (s, 3H), 3.10 (d, 1H, *J* = 17.9 Hz), 3.69 (d, 1H, *J* = 17.2 Hz), 3.81 (s, 3H), 4.41-4.62 (brs, 1H), 6.86, (d, 2H, *J* = 8.9 Hz), 7.85 (d, 2H, *J* = 8.9 Hz); $^{13}$C-NMR ($CDCl_3$) δ 24.4, 25.1, 46.7, 55.5, 78.3, 113.8, 129.2, 130.7, 164.1, 199.01, 213.7; IR (neat) 3461, 1711, 1675 cm$^{-1}$; Anal. Calcd. for $C_{13}H_{17}O_4$: C, 66.09; H, 6.83. Found: C, 65.99; H, 6.70. HRMS (FAB); Exact mass calcd. for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1134. HPLC, Daicel Chiralcel ADH, hexane:$^{i}$PrOH = 19:1, flow rate = 0.5 mLmin$^{-1}$: *tr* = 53.1 min (major enantiomer), *tr* = 57.0 min (minor enantiomer).



**1-(4-chlorophneyl)-3-hydroxy-3-methylpentane-1,4-dione (4.43)**

Obtained in 90% and 82% *ee*; $^{1}$H-NMR ($CDCl_3$) δ 1.31 (s, 3H), 2.30 (s, 3H), 3.14 (d, 1H, *J* = 18.0 Hz), 3.69 (d, 1H, *J* = 18.0 Hz), 4.21-4.49 (brs, 1H), 7.38 (d, 2H, *J* = 8.9 Hz), 7.81 (d, 2H, *J* = 8.9 Hz); $^{13}$C-NMR ($CDCl_3$) δ 23.9, 24.8, 46.7, 77.9, 128.7, 129.4, 134.1, 140.1, 199.01, 212.8; IR (neat) 3462, 1714, 1683 cm$^{-1}$; HRMS (FAB); Exact mass calcd. for $C_{12}H_{14}ClO_3$ $[M+H]^+$, 241.0631. Found 241.0635. HPLC, Daicel Chiralcel ADH, hexane:$^{i}$PrOH = 19:1, flow rate = 0.5 mLmin$^{-1}$: *tr* = 33.1 min (major enantiomer), *tr* = 36.8 min (minor enantiomer).



**3-Hydroxy-3-methyl-1-phenylhexane-1,4-dione (4.44) and 3-ethyl-3-hydroxy-1-phenylpentane-1,4-dione (4.45) (mixture)**

$^{1}$H-NMR ($CDCl_3$) (spectral data reported together; 1H of (**4.45**) is given as 1H integration whereas 1H for (**4.44**) is given as 7H (*i.e.*, ration is 7:1)) 0.86 (t, 3H, *J* = 7.6 Hz), 1.02 (t, 21H, *J* = 6.9 Hz), 1.30 (s, 21H), 1.69-1.78 (m 2H), 2.28 (s, 3H), 2.68-2.81 (m, 14H), 3.14 (d, 7H, *J* = 17.9 Hz), 3.26 (d, 1H, *J* = 17.2 Hz), 3.59 (d, 1H, *J* = 17.2 Hz), 3.77 (d, 7H, *J* = 17.8 Hz), 4.26-4.48 (brs (with br side peak), 7.3H), 7.27-7.33 (brm, 2H), 7.40 (t, 14H, *J* = 8.3 Hz), 7.53 (appt, 8H, *J* = 7.6 Hz), 7.87 (appd, 16H, *J* = 7.9 Hz); $^{13}$C-NMR ($CDCl_3$) (for major product) δ 24.4, 25.1, 46.7, 55.5, 78.3, 113.8, 129.2, 130.7, 164.1, 199.01, 213.7; IR (neat) 3462, 1709, 1672 cm$^{-1}$;

Anal. Calcd. for $C_{13}H_{17}O_4$: C, 66.09; H, 6.83. Found: C, 65.99; H, 6.70. HRMS (FAB); Exact mass calcd for $C_{13}H_{17}O_3$ $[M+H]^+$, 221.1178. Found 237.1176.

HPLC, Daicel Chiralcel ADH, hexane:$^i$PrOH = 9:1, flow rate = 0.2 mLmin$^{-1}$: *tr* = 47.6 min (major enantiomer for (**4.44**)), *tr* = 53.6 min (minor enantiomer for (**4.44**)), *tr* = 51.4 min (major enantiomer for (**4.45**)) and *tr* = 57.2 min (minor enantiomer for (**4.45**)).

# Part III

A Transannular Mannich Approach to Polycyclic Alkaloids: Synthetic Studies on the Cylindricine Alkaloids

Part III

# CHAPTER 1
# Transannular Reactions - An Overview

## 1.1 - Introduction

Intramolecular processes can in general be divided into two different categories: either the functional groups undergoing reaction are linked *via* one tether, a conventional intramolecular reaction (*i.e.*, from (**1.1**) to (**1.2**)), or the reactive functional groups are tethered to each other at both termini, a transannular reaction (*i.e.*, from (**1.3**) to (**1.4**)) (Figure 1.1).

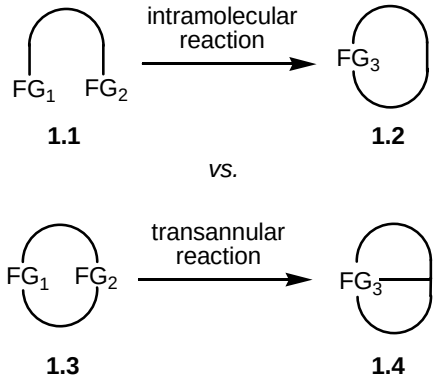



**Figure 1.1** Intramolecular and transannular reactions.

Transannular reactions can display significant advantages over their intermolecular and conventional intramolecular counterparts and thus have the potential to provide unique solutions in synthesis. Because medium- (*i.e.*, 8-11) and (to a lesser extent) large-size (*i.e.*, 12 or higher) alicyclic molecules can adopt stable puckered conformations where opposite sides of the ring are close to each other, bond forming processes can be greatly favored in these types of ring systems, taking place under often surprisingly mild conditions.[1.1] Lower reaction temperatures, together with the constraints imposed by the connecting ring, provide a unique opportunity for achieving chemo-, regio- and stereoselectivity. Furthermore, by using more forcing conditions one can in principle carry out reactions that would be doomed to failure in the intermolecular and conventional intramolecular versions.

Once the feasibility of employing a transannular reaction has been recognized, the main challenge often becomes the synthesis of the macrocyclic precursor. This has traditionally been a major problem, however, several methods are now available for the efficient preparation of medium and large rings,[1.2] and so the problem of the precursor synthesis should no longer present a serious concern.

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[1.1] For a general reference see: Eliel, S. T.; Wilen, S. H. in "Stereochemistry of Organic Compounds" **1994**, John Wiley & Sons, New York.

[1.2] For some reviews on macrocyclizations see: (a) Roxburgh, C. *Tetrahedron* **1995**, *51*, 9767. (b) Paterson, I.; Norcross, R. D. *Chem. Rev.* **1995**, *95*, 2041. (c) Williams, A. S. *Synthesis* **1999**, *10*, 1707.

Another apparent obstacle to a more generalized use of transannular processes is the somewhat limited ability to predict the regio- and stereochemical aspects of such reactions. Although forecasting the selectivity of chemical reactions by inspecting molecular models corresponding either to the starting materials or to the product has been successful for some transannular reactions,[1.3] the truly significant geometries in kinetically driven reactions are the transition state structures. The problem can become even more complicated when other factors than sterics, namely stereoelectronics, are at play. For example, in transannular Diels-Alder (TADA) reactions, the *endo* effect can either antagonize or act in a synergetic manner with all the other effects and thus the ratio of TADA adducts can be rather difficult to predict. As computational methods progress and become more widely available, particularly transition-state molecular modeling, it is anticipated that predictive power will emerge, allowing transannular reactions to be incorporated with confidence in synthetic planning and enabling synthetic chemists to develop new and innovative strategies of molecular construction.

(d) Griesbeck, A. G.; Henz, A.; Hirt, J. *Synthesis* **1996**, 1261. (e) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.For selected examples see: (f) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 6112. (g) McMurry, J. E.; Matz, J. R. *Tetrahedron Lett.* **1982**, *23*, 2723. (h) Takahashi, T.; Nemoto, H.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 2005. (i) Still, W. C.; Mobilio, D. J. *J. Org. Chem.* **1983**, *48*, 4875. (j) Deslongchamps, P. *Aldrichim. Acta* **1984**, *17*, 59. (k) Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560. (l) Corey, E. J. *J. Am. Chem. Soc.* **1978**, *100*, 4620. (m) Mukaiyama, T. *Chem. Lett.* **1976**, 49. (n) Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394. (o) Masamune, S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. (p) Inaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (q) Mitsunobu, O. *Synthesis* **1981**, 1. (r) Marshall, J. A. *J. Org. Chem.* **1998**, *53*, 1616. (s) Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345. (w) Smith, A. B. III; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095. (t) Nicolau, K. C. J. Am. Chem. Soc. 1993, 115, 4419. (u) Lipton, M. A. *Tetrahedron Lett.* **1993**, *34*, 7899. (v) Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 2733. (u) Marshall, J. A.; DeHoff, B. S.; Crooks, S. L. *Tetrahedron Lett.* **1987**, *28*, 527.

[1.3] For selected examples where the stereochemical outcome of reactions (*e.g.*, reductions, enolate alkylations and cuprate additions) in macrocycles was successfully predicted based on simple conformational analysis see: (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (b) Neeland, E.; Ounsworth, J. P.; Sims, R. J.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 35.

## 1.2 – Selected Uses of Transannular Reactions in Organic Synthesis

Until fairly recently, the use of transannular reactions in organic synthesis was, to a great extent, limited to electrophilic cyclizations of cycloalkenes.[1.4] Lately, however, several examples of different transannular processes, ranging from radical cyclizations, cycloisomerizations to cycloadditions, have been incorporated as key steps in complex total syntheses. This has been particularly significant in (often postulated) biomimmetic-inspired approaches, suggesting that Nature extensively uses transannular reactions in the biosynthesis of complex polycyclic systems. Some representative examples of such transannular processes are presented bellow with the focus being put on the formation of the macrocycle and the transannular step.

In the last decade several groups have explored different elegant radical cascades strategies implying one or more cyclization(s) to access polycyclic natural product skeletons.[1.5] Malacria and co-workers carried out a biomimetic, diastereoselective synthesis of racemic *epi*-elludol (**1.7**) from cycloundecadienyne (**1.6**) *via* a intramolecular-transannular radical cascade.[1.6] The required highly strained eleven-membered ring precursor (**1.6**) was efficiently prepared in 88% yield as a mixture of diastereomers from aldehyde (**1.5**) using a Nozaki-Hiyama-Kishi type ring-closure.[1.7] Under classical $Bu_3SnH$-AIBN conditions the 4,6,5-cyclic framework was produced. Functional group manipulation then delivered the natural product (**1.7**) in good overall yield (47%) (Scheme 1.1).

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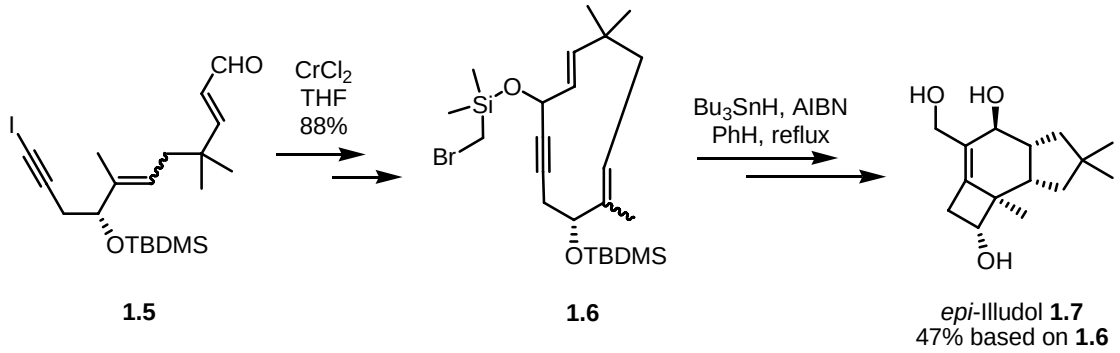
[1.4] For reviews see: (a) Cope, A. C.; Martin, M. M.; McKervey, M. A., Q. Rev., Chem. Soc. 1966, 20, 119. (b) Prelog, V.; Traynham, J. G. in "Molecular Rearrangements" (de Mayo, P. ed.) **1963**, Wiley, New York.

[1.5] For selected examples of different strategies see: i) **intramolecular-transannular** (a) Winkler, J. D.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708. (b) Aïssa, C.; Dhimane, A.-L.; Malacria, M. *Snylett* **2000**, 1585. (c) Winkler, J. D.; Sridar, V. *Tetrahedron Lett.* **1988**, *29*, 6219. ii) **transannular-intramolecular** (d) Curran, D. P.; Shen, W. *Tetrahedron* **1993**, *49*, 755. (e) Booker-Milburn, K. I.; Dainty, R. F. *Tetrahedron Lett.* **1998**, *39*, 5097. iii) **macrocyclization-transannular** (f) Pattenden, G.; Wiedenau, P. *Tetrahedron Lett.* **1997**, *38*, 3647. (g) Begley, M. J.; Pattenden, G.; Smithies, A. J.; Tapolczay, D.; Walter, D. S. *J. Chem. Soc. Perkin Trans 1* **1996**, 21. iv) **completely transannular** (h) Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1993**, *115*, 7926. (i) Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057.

[1.6] Elliot, M. R.; Dhimane, A.-L., Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 3427.

[1.7] (a) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. (b) Jin, H.; Uenishi, J.-I.; Christ, W, J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (c) Crevisy, C.; Beau, J.-M. *Tetrahedron Lett.* **1991**, *32*, 3171. (d) Lu, Y.-F.; Harwig, C. W.; Fallis, A. G. *J. Org. Chem.* **1993**, *58*, 4202. (e) Elliot, M. R.; Dhimane, A.-L., Hamon, L.; Malacria, M. Eur. *J. Org. Chem.* **2000**, 155.



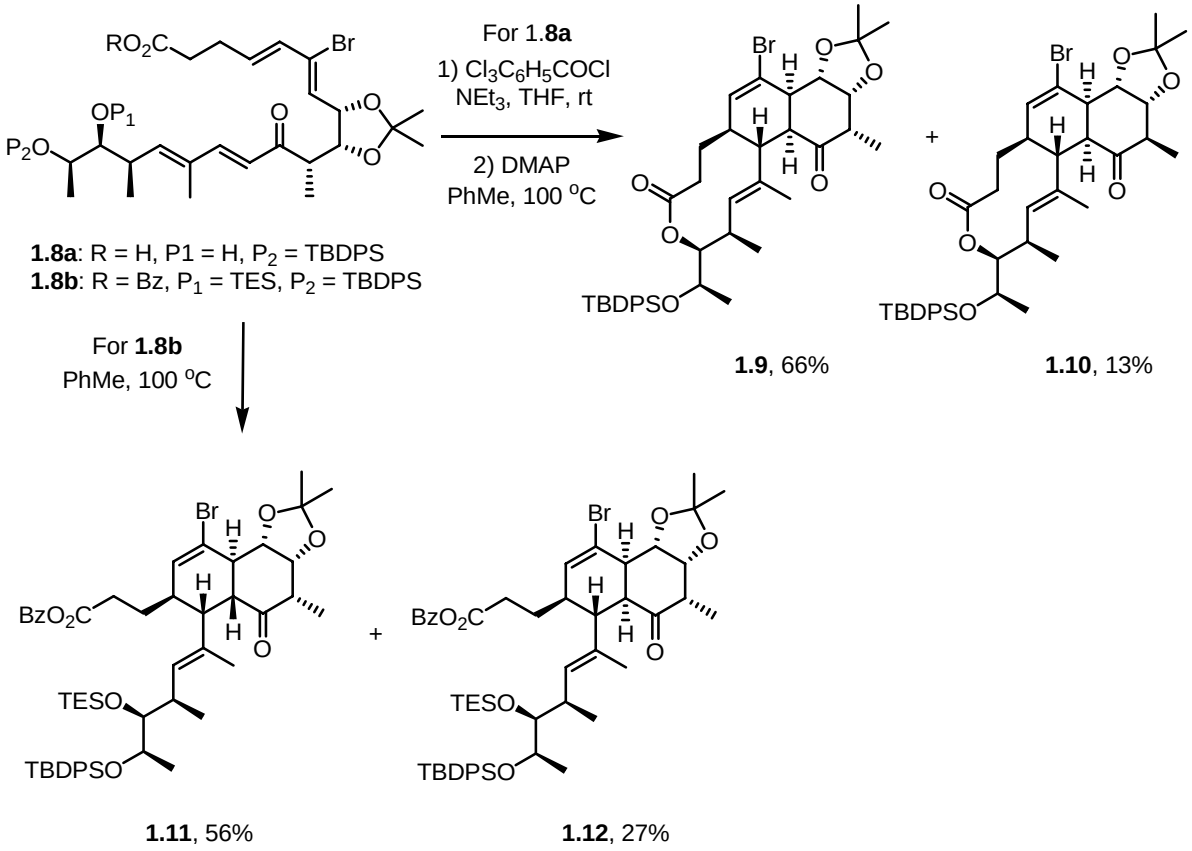

**Scheme 1.1** Preparation of *epi*-illudol (**1.7**) based on a transannular radical cyclization.

One of the most powerful tools to emerge recently for the construction of complex polycyclic systems are transannular cycloaddition reactions, specially the transannular Diels-Alder (TADA). The Deslongchamps group in particular has clearly demonstrated the value of the TADA reaction is synthesis.[1.8,1.9] TADA reactions often complement conventional intramolecular Diels-Alder variants (IMDA) since in cases where IMDA reactions are unsuccessful (*e.g.*, due to poor dienophiles[1.8h,n,p] or difficult dienes[1.8m,n]) or give the wrong regio- or stereochemistry, the TADA often proceeds efficiently. An example where is possible to compare the TADA with the

[1.8] For selected examples see. (a) Marsault, E.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 3317. (b) Toro, A.; L'Heureux, A.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 2737, (c) Lavoie, R.; Ouellet, S. G.; Dallaire, C.; Dory, Y. L.; Toro, A.; Deslongchamps, P. *Tetrahedron* **2000**, *56*, 5509. (d) Toro, A.; Nowak, P.; Deslongchamps. P. *J. Am. Chem. Soc.* **2000**, **122**, 4526. (e) Fortin, S.; Barriault, L.; Dory, Y. L.; Deslongchamps, P. *J. Am. Chem. Soc.* **2001**, *123*, 8210. (f) Baettig, K.; Pitteloud, R.; Deslongchamps, P.; *Tetrahedron Lett.* **1987**, *28*, 5249. (g) Baettig, K.; Marinier, A.; Pitteloud, R.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5253. (h) Bérubé, G.; Deslongchamps, P. *Tetrahedron Lett*. **1987**, *28*, 5255. (j) Deslongchamps, P. *Pure & Appl. Chem.* **1992**, *64*, 1831. (k) Couturier, M.; Deslongchamps, P. *Synlett* **1996**, 1140. (l) Marinier, A.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 2351. (m) Marinier, A.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 6215. Couturier, M.; Dory, Y. L.; Rouillard, F.; Deslongchamps, P. *Tetrahedron* **1998**, *54*, 1529. (n) Toro, A.; Lemelin, C.-A.; Preville, P.; Belanger, G.; Deslongchamps, P. *Tetrahedron* **1999**, *55*, 4655. (o) Toro, A.; Wang, Y.; Deslongchamps, P. *Tetrahedron Lett.* **1999**, *40*, 2765. (p) Belanger, G.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 285.

[1.9] For selected contributions from other groups see: (a) Takahashi, T.; Katsuya, S.; Doi, T.; Tsuji, J. *J. Am. Chem. Soc.* **1988**, *110*, 2674. (b) Takahashi, T.; Sakamoto, Y.; Doi, T. *Tetrahedron Lett.* **1992**, *33*, 3519. (c) Woody, J. L.; Porco, J. A.; Taunton, J.; Lee, A. Y.; Vlardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898. (d) Marshall, J. S.; Wang, X.-J. *J. Org. Chem.* **1992**, *57*, 3387.; Jung, S. H.; Lee, Y.; S.; Park, H.; Kwon, D.-S. *Tetrahedron Lett.* **1995**, *36*, 1051. (e) Roush, W.; R.; Works, A.; B. *Tetrahedron Lett.* **1996**, *37*, 8065. (f) Moriyama, S.; Karakasa, T.; Inoue, T.; Kurashima, K.; Satsumabayashi, S.; Saito, T. *Synlett* **1996**, 72. (g) Begley, M. J.; Grove, J. F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 861. (h) Evans, D.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787.

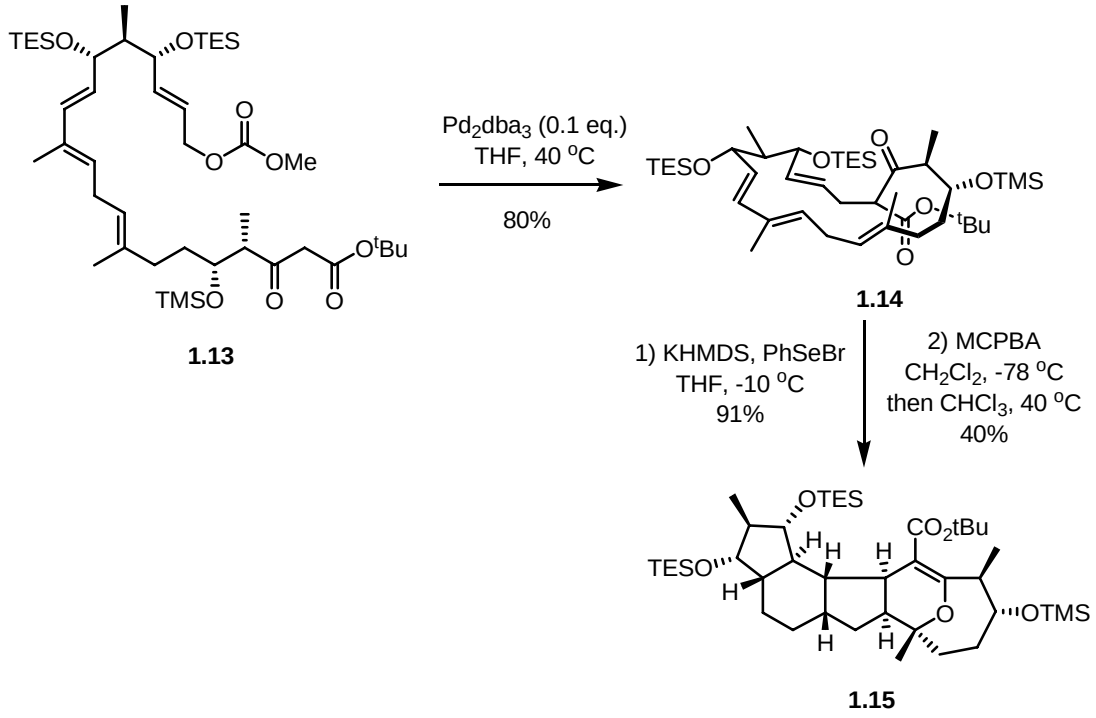
corresponding IMDA was reported by Roush and co-workers in their studies on the synthesis of Nargenicin $A_1$ (Scheme 1.2).[1.10] The keys steps in the synthesis are Yamaguchi macrolactonization[1.2p] of hydroxy acid (**1.8a**) and the facile TADA reaction of the corresponding 18-membered macrolide. This sequence provides the desired cis-fused tricycle (**1.9**) in 66% yield, along with 14% yield of tricycle (**1.10**) which is epimeric at C-10. In contrast, the IMDA reaction of seco ester (**1.8b**) provided a mixture of trans-fused (**1.11**) in 56% yield and the desired cis-fused cycloadduct (**1.12**) in only 27% yield.




**Scheme 1.2** The TADA and IMDA as key steps in a planned total synthesis of Nargenicin $A_1$.

[1.10] Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502.

The Sorensen group disclosed an impressive example of a double transannular Diels-Alder reaction in the synthesis of the hexacycle FR182877 (Scheme 1.3).[1.11] The macrocycle precursor (**1.14**) was obtained in high yield (80%) from (**1.13**) using the Trost-Tsuji conditions.[1.12] After some functional group manipulation, required to introduce unsaturation between the two carbonyl functions, the obtained macrocycle (not shown) underwent a tandem TADA/transannular hetero-Diels Alder transforming a 19-membered ring carbocycle to the complex pentacycle (**1.15**) possessing no less than seven new contiguous stereocenters.

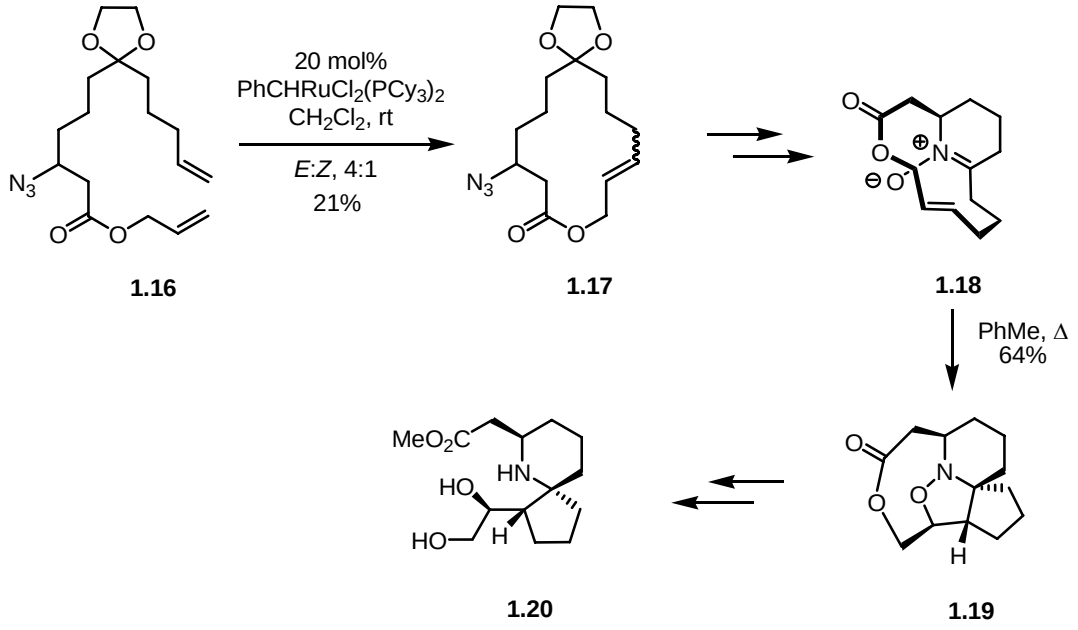



**Scheme 1.3** A double TADA in the preparation of pentacycle (**1.15**).

[1.11] (a) Vosburg, D. A.; Vanderwal. C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, 5393. (b) Vosburg, D. A.; Vanderwal. C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552 (c) Sorensen, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 3225. For a similar approach to FR182877 see also ref.1.9h.

[1.12] (a) Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173. (c) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809. (d) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361.

White and co-workers recently reported the synthesis of the azaspirocyclic core (**1.20**) of pinnaic acid *via* the use of a stereospecific transannular nitrone cycloaddition.[1.13,1.14] Ring closing metathesis (RCM)[1.15] of azide (**1.16**) using Grubbs catalyst afforded the 14-membered macrocycle (**1.17**) in 21% yield as a *E*:*Z* mixture. The latter was then converted into nitrone (**1.18**) which, upon thermolysis, underwent a stereospecific transannular nitrone-olefin [3+2] cycloaddition to afford the tetracycle (**1.19**) which was easily converted to the key intermediate (**1.20**). Notably, also here the conventional intramolecular nitrone cycloaddition gave isoxazolidines of incorrect relative configuration.



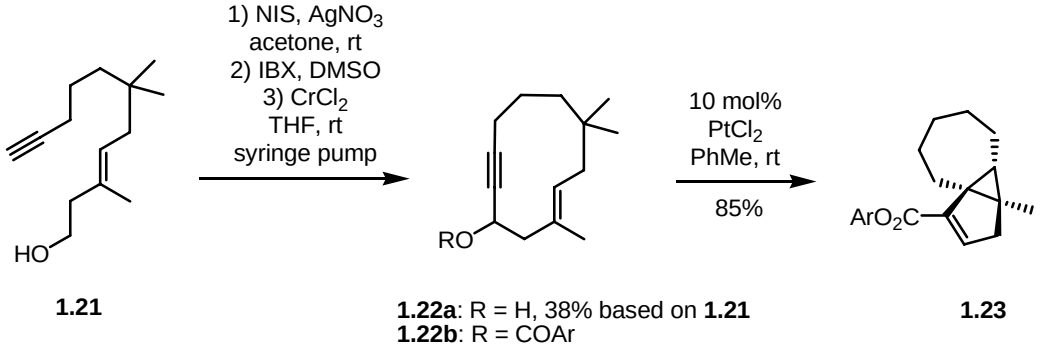

**Scheme 1.4** Stereocontrolled entry to the spirocyclic core of pinnaic acid (**1.20**) *via* a transannular nitrone cycloaddition.

[1.13] White, J. D.; Blakemore, P. R.; Korf, E. A.; yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413.

[1.14] For examples of transannular cycloadditions in which the nitrone is external to the ring see: (a) Baggioline, E. G.; Lee, H. L.; Pizzolato, G.; Uskokovic, M. *J. Am. Chem. Soc.* **1982**, *104*, 6460. (b) Mihailovic, M. L.; Rajkovic, M. M.; Lorenc, L. B.; Pavlovic, V. D.; Milovanovic, A. Z.; Tinant, B.; Declercq, J.-P. *Tetrahedron* **1996**, *52*, 11995.

[1.15] Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

Organometallic reactivities have been rarely used in a transannular fashion.[1.16] One such example is the transannular $PtCl_2$-catalyzed cycloisomerization of 1,5-enyne (**1.22b**) recently reported by Dhimane, Fensterbank, Malacria and co-workers.[1.17] The 1,5-enyne macrocycle (**1.22a**) was obtained in 38% from alcohol (**1.21**) using a Nozaki-Hiyama-Kishi-Takai Cr(II)-mediated process.[1.18] Treatment of the benzoate (**1.22b**) with a catalytic amount of $PtCl_2$ afforded racemic tricyclic (**1.23**) in a diastereoselective manner and high yield (85%).




**Scheme 1.5** $PtCl_2$-catalysed transannular cyclization of cycloundecenyne (**1.22b**).

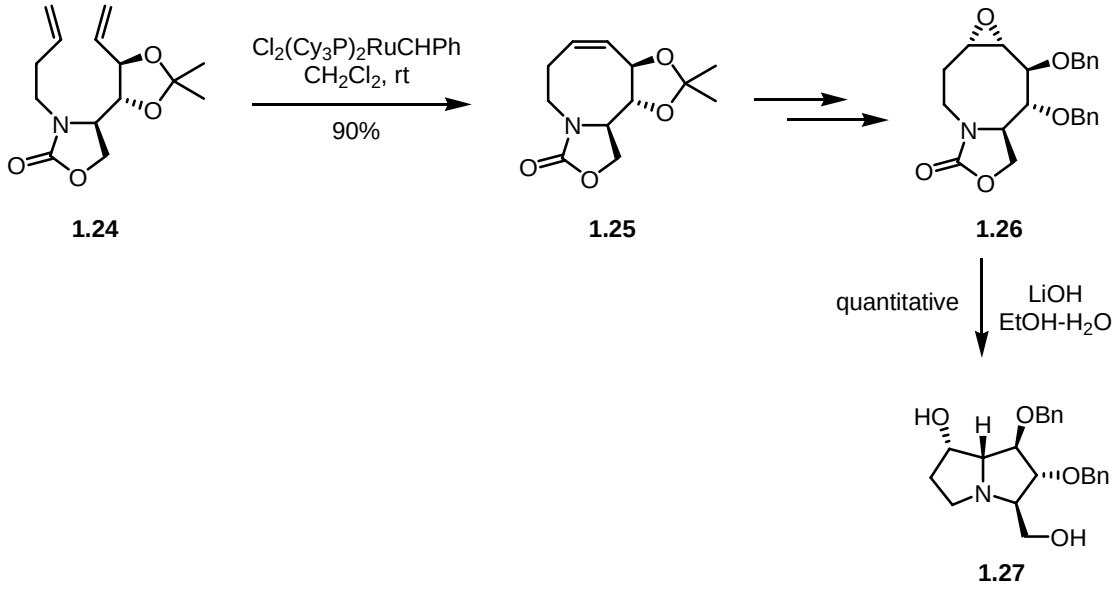
White and Hrnciar achieved the total synthesis of (+)-australine in a sequence that had as key steps the preparation of azacyclooctene (**1.25**), obtained from diene (**1.24**) *via* RCM with Grubbs catalyst, and a base-induced transannular ring-closing step of oxazolidinone (**1.26**) (Scheme 1.6).[1.19]

[1.16] For (rare) examples see: (a) Transannular oxypalladation: Sasaki, T.; Kanematsu, K.; Kondo, A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2516. (b) Transannular [3+2] cycloaddition: Yamago, S.; Nakamura, E. *Tetrahedron* **1986**, *45*, 3081. (c) Transannular cyclopalladation: Ohe, K.; Miki, K.; Yanagi, S.-I.; Tanaka, T.; Sawada, S.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3627.

[1.17] Blaszykowski, C.; Harrak, Y. H.; Goncalves, M.-H.; Cloarec, J.-M.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 3771.

[1.18] (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Okude, Y.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1977**, 3829. (c) Cintas, P. *Synthesis* **1992**, 248. (d) Fürstner, A. *Pure Appl. Chem.* **1998**, *70*, 1071. (e) Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5585.

[1.19] (a) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129. See also (b) White, J. D. Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359.




**1.24** **1.25** **1.26** **1.27**

**Scheme 1.6** Transannular ring-opening of epoxide (**1.26**).

# CHAPTER 2
# A Transannular Mannich Approach to Polycyclic Alkaloids

## 2.1 - Introduction

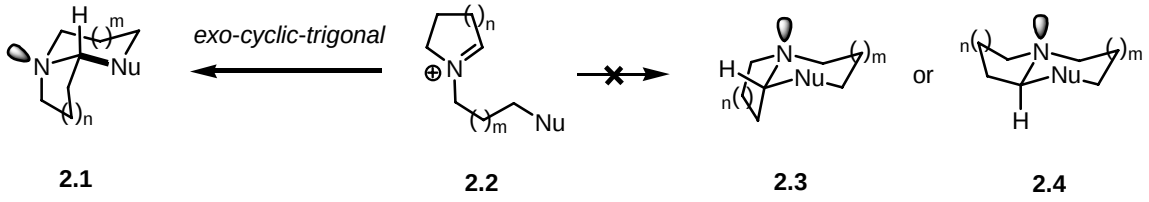
The development of methodology that allows the efficient generation of complex polycyclic skeletons from easily accessible starting materials is an important goal in organic synthesis.

Among the few organic reactions that are noteworthy for the potential to generate complexity in their products is the intramolecular Mannich (IMM) reaction.[2.1] The IMM reaction refers to the addition of a C-H activated carbon nucleophile (*e.g.*, aldehydes or ketones, enol ethers, carboxylic acid derivatives, *β*-dicarbonyl compounds, arenes, etc.) to an iminium ion in an intramolecular fashion. The regioselectivity of the IMM is expected to be in accordance with the Baldwin selection rules for ring closure.[2.2] Furthermore, the stereoselectivity in the addition to iminium ions is (often) governed by stereoelectronic factors in that the addition reaction proceeds so that there is an antiperiplanar arrangement between the incoming nucleophile and the developing electron pair in the product.[2.3] Thus, the IMM cyclization of iminium ion (**2.2**) is expected to preferentially deliver the *cis*-conformer (**2.1**) initially, even though the alternate *cis*-(**2.3**) conformer or the *trans*-(**2.4**) system may be more stable (Scheme 1.1).

[2.1] For selected general reviews on the Mannich reaction see: (a) Arend, M.; Westermann, B.; Rish, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044. (b) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791. (c) Tramontini, M. *Synthesis* **1973**, 703. For a review on the IMM reaction see: (d) Overman, L. E.; Ricca, D. J. in "Comprehensive Organic Synthesis" (Trost, B. M.; Fleming, I., ed.) **1991**, *2*, 1007, Pergamon, Oxford. For selected reviews on the vinylogous Mannich reaction see: (e) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895. (f) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221. (g) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

[2.2] (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

[2.3] Deslongchamps, P. in "Stereolelectronic Effects in Organic Chemistry"**1983**, Pergamon, Oxford.

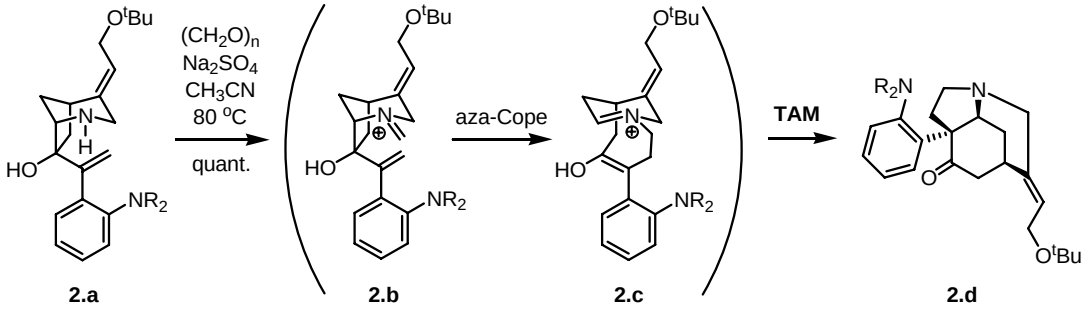



**Scheme 1.1** (Intramolecular) addition of nucleophiles to iminium ions.

The predictable regio- and stereoselectivity of the IMM has contributed to its popularity among synthetic organic chemist, as shown by the countless syntheses of cyclic nitrogen compounds where it has already been used.[2.4] In contrast, the transannular Mannich (TAM) variation remains virtually unexplored (Scheme 2.2).[2.5,2.6]

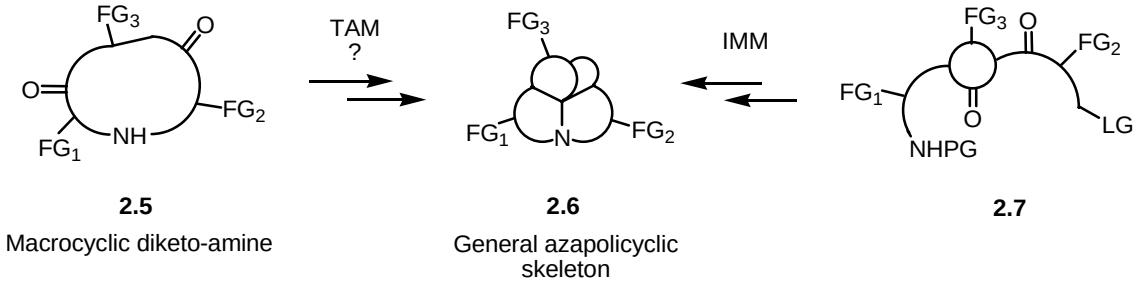
[2.4] For selected examples see: (a) Corey, E. J.; Balanson, R. D. *J. Am. Chem. Soc.* **1974**, *96*, 6516. (b) Carruthers, W.; Moses, R. C. *J. Chem. Soc., Chem. Commun.* **1987**, 509. (c) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028. (d) Heerding, D. A.; Hong, C. Y.; Kado, N.; Look, G. C.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 6947.

[2.5] It is interesting to note that, to some extent, the feasibility of TAM processes has already been indirectly established in the form of the tandem cationic aza-Cope/Mannich cyclization.[2.7] A celebrated example, by Overman and co-workers, is the total synthesis of (-)-strychnine.[2.7a] Treatment of azabicyclooctane (**2.a**) with paraformaldehyde afforded the diamine (**2.d**) in quantitative yield as a single diastereoisomer, through a cascade aza-Cope rearrangement of iminium ion (**2.b**) and a diastereoselective TAM cyclization of the medium-size 9-membered iminium ion (**2.c**) (Scheme 2.A).



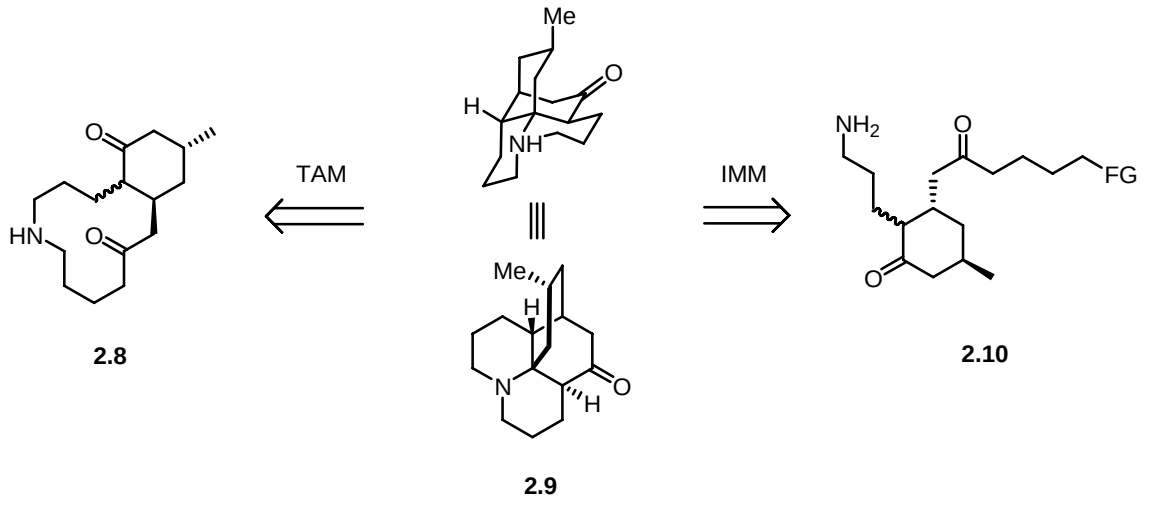

**Scheme 2.A** Tandem aza-Cope/Mannich cyclization of cyclooctane (**2.a**).

[2.6] (a) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776. (b) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis Jr., R. W.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966. (c) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598. (d) Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685.




**Scheme 2.2** IMM and TAM reactions in the construction of azapolicyclic frameworks.

Notably, TAM processes have been previously *considered* in the synthesis of azapolycyclic alkaloids but surprisingly were never implemented. For example, Heathcock and co-workers recognized that lycopodine (**2.9**) could arrive *via* a TAM condensation of the macrocycle (**2.8**) (Scheme 2.3).[2.7] Although this analysis would retrosynthetically transform a tetracyclic system into a bicyclic system, and thus result in a considerable structural simplification according to some criteria, this strategy was never put into practice because "the postulated reactant (**2.8**) is more complicated than lycopodine (**2.9**) in having a 12-memberd ring".




**Scheme 2.3** Two Mannich-based approaches to lycopodine (**2.9**).

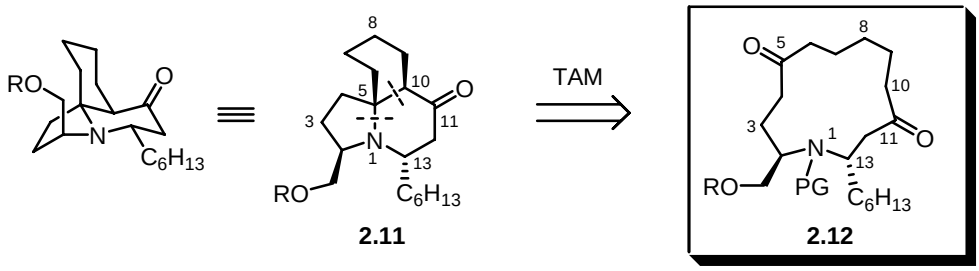
Considering the advantages often associated with the use of transannular reactions in synthesis (*vide* Chapter 1), it is realistic to expect that the TAM reaction, if feasible, would constitute a powerful approach for the construction of azapolycyclic frameworks. We set ourselves to explore this possibility.

[2.7] Heathcock, C. H.; Kleinman, E.; Binkley, E. *J. Am. Soc. Chem.* **1982**, *104*, 1054.

## 2.2 – Project Description

It is the goal of this project to investigate the hypothesis that the azapolycyclic framework of certain alkaloids can be accessed *via* a TAM of conveniently functionalized macrocycle precursors.

The cylindricine alkaloids (**2.11**), by virtue of their tricyclic skeleton, were chosen as targets for testing the proposed novel methodology. A simplified retrosynthetic analysis of the general cylindricine skeleton based on the key TAM step is shown in Scheme 2.4.[2.8] This analysis is interesting and unusual in that two simultaneous bond disconnections lead to the 13-membered macrocycle (**2.12**). Thus, this analysis seems to contradict the generally accepted guidelines according to which the retrosynthetic generation of such "difficult" ring sizes is not strategically advisable.

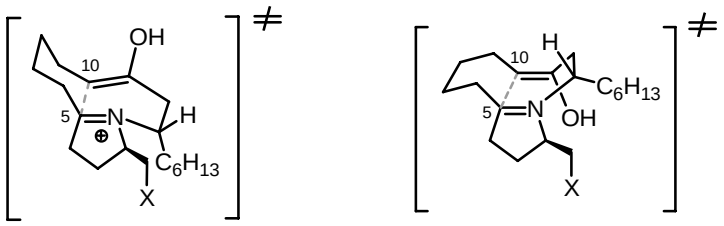



**Scheme 2.4** The TAM approach to the tricyclic skeleton of the cylcindricines (**2.11**).

However, if an efficient method for preparing the 13-membered ring (**2.12**) was available, then the tricyclic skeleton of the target could be assembled *in a single operation*, *via* a TAM. The deprotected macrocyclic amine (**2.12**) is predicted to chemoselectively condensate with the C-5 ketone to afford the corresponding 5-membered iminium ion, which can then undergo a TAM reaction with enol form of the C-11 ketone.

Formation of the correct configuration at C-5 and C-10 will depend upon steric (attack on the less-hindered *Re*-face of the iminium ion) and conformational (*Re versus Si* enol faces and *E versus Z* enol geometries) factors and these remain open questions (Figure 2.1).

[2.8] (a) Warren, S. in "The Disconnection Approach" **1996**, Wiley, New York. (b) Warren, S. in "Designing Organic Syntheses – A Programmed Introduction to the Synthon Approach" **1994**, Wiley, Cambridge.




*Re* iminium to *Re* enolate (*Z*)
chair

*Re* iminium to *Si* enolate (*E*)
boat

**Figure 2.1** Possible transition states for formation of the C-5—C-10 bond leading to the correct configuration.

# CHAPTER 3
# The Cylindricine Alkaloids - An Overview

## 3.1 - Isolation and Structure

The cylindricines were first isolated in the early 1990s by Blackman and co-workers from the Tasmanian ascidian[3.1] *Clavelina cylindrical*.[3.2] The structures of the two most abundant members of this family of marine alkaloids, cylindricines A (**3.1a**) and B (**3.1b**), were established by spectral analysis and X-ray crystallography of the corresponding picrates.[3.1a] These studies reveled that both these natural products have a tricyclic framework with a *cis*-fused 1-azadecalin A/B-ring system, but whereas cylindricine A has a pyrroloquinoline skeleton, cylindricine B possess a pyridoquinoline framework. Interestingly, both cylindricines A and B produce the same 3:2 equilibrium mixture upon standing, presumably due to interconversion *via* the aziridinium intermediate (**3.2**). [3.2a] In addition to these alkaloids, other minor metabolites having the basic cylindricine A-type skeleton but with small structural differences were later isolated. Examples of these include cylindricines C (**3.1c**) to F (**3.1f**), which possess different functionalities at C-14. Cylindricines H (**3.1h**) can be seen as the acetate of the reduction product of cylindricine F (**3.1f**) whereas cylindricine I (**3.1i**) is the analogous isothiocyanate. Cylindricine J (**3.1j**) is a reduced isothiocyanate analogue of cylindricine B (**3.1b**). Finally, cylindricine K (**3.1k**) contains an $\alpha,\beta$-unsaturated ketone functionality incorporated into the A-ring (Figure 3.1).

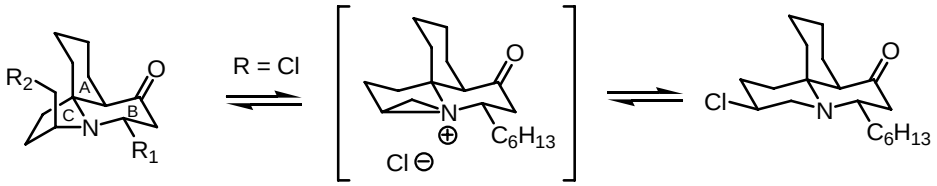
Regarding the absolute configurations of the cylindricines, these have not yet been established since the optical rotations of these compounds were not measured during the structural studies. Until re-isolation of these metabolites, the question of their absolute configuration will remain unanswered.[3.3] Recent enantioselective total syntheses of these natural products allowed the conclusion that the enantiomeric

[3.1] Ascidians are marine invertebrates of the phylum *Chordata*, subphylum *Tunicata*.

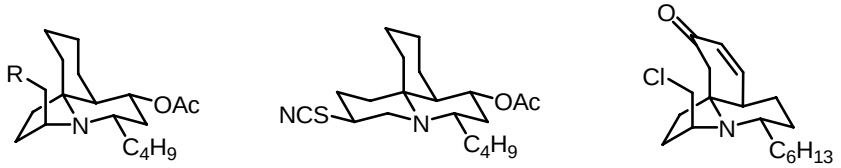
[3.2] (a) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645. (b) Li, C.; Blackman, A. J *Aust. J. Chem.* **1994**, *47*, 1355. (c) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1995**, *48*, 955.

[3.3] It has been speculated, on the basis of recent enantioselective syntheses of a closely related alkaloid, lepadiformine (**3.4a**), that the cylindricine alkaloids in the natural series are enantiomeric to the structures drawn in Figure 3.1.

series presented in the original paper by Blackman corresponds to the (-)-cylindricines.




**3.1a**: Cylindricine A, $R_1 = C_6H_{13}$, $R_2$ = Cl **3.2** **3.1b**: Cylindricine B
**3.1c**: Cylindricine C, $R_1 = C_6H_{13}$, $R_2$ = OH
**3.1d**: Cylindricine D, $R_1 = C_6H_{13}$, $R_2$ = OMe
**3.1e**: Cylindricine E, $R_1 = C_6H_{13}$, $R_2$ = OAc
**3.1f**: Cylindricine F, R1 = $C_6H_{13}$, $R_2$ = SCN
**3.1g**: Cylindricine G, $R_1 = C_4H_9$, $R_2$ = SCN




**3.1h**: Cylindricine H, $R_2$ =SCN **3.1j**: Cylindricine J **3.1k**: Cylindricine K
**3.1i**: Cylindricine I, $R_2$ = NCS

**Figure 3.1** The (-)-cylindricine alkaloids.

Structurally related alkaloids to the cylindricines include fasicularin (**3.3**)[3.4,3.5] and the lepadiformines (**3.4a**) and (**3.4b**).[3.6,3.7] These differ mainly from the cylindricines in that they possess a *trans*-1-azadecaline A/B ring system (Figure 3.2).

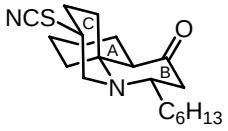
---

[3.4] For the isolation of fasicularin (**3.3**), see: Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K. *Tetrahedron Lett.* **1997**, *38*, 363.

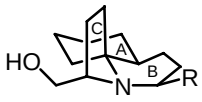
[3.5] For selected total syntheses of fasicularin (**3.3**) see: (a) Abe, H.; Aoyagi, S. Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583. (b) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473. (c) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2002**, *4*, 331. (d) Dake, G. R.; Fenster, M. D. B.; Hurley, P. B.; Patrick, B. O. *J. Org. Chem.* **2004**, *69*, 5669.

[3.6] For isolation of lepadiformines (**3.4a**) and (**3.4b**), see: (a) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691. (b) Jugé, M.; Grimaud, N.; Biard, J. F.; Sauviat, M. P.; Nabil, M.; Verbist, J. F.; Petit, J.-Y. *Toxicon* **2001**, *39*, 1231.

[3.7] For an account on efforts involving the synthesis of lepadiformines (**3.4a**) and (**3.4b**), see: (a) Weinreb, S. M. *Acc. Chem. Res.* **2003**, *36*, 59. (b) Kibayashi, C.; Aoyagi, S.; Abe, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2059. For selected total synthesis of the lepadiformine alkaloids see: (c) Werner, K. M.; De Los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686. (d) Werner, K. M.; De Los Santos, J. M.; Weinreb, S. M. *J. Org. Chem.* **1999**, *64*, 4865. (e) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369. (f) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*,




**3.3**: Fasicularin




**3.4a**: Lepadiformine, R = $C_6H_{13}$
**3.4b**: Lepadiformine B, R = $C_4H_{13}$

**Figure 3.2** Structures of fasicularin (**3.3**) and lepadiformine (**3.4**).

## 3.2 – Biological Activity

No significant biological activity has been reported for any of the cylindricines other than that a 30 μM solution of the 3:2 equilibrium mixture of cylindricines A (**3.1a**) and B (**3.1b**) was found to cause significant mortality in the brine shrimp bioassay.[3.2] However, it should be appreciated that the closely related alkaloids fasicularin (**3.3**) and lepadiformines (**3.4a**) and (**3.4b**) were found to exhibit biological activity against a DNA-repair-deficient of yeast strain and to inhibit growth of murine leukemia and human solid tumor cell lines.[4.4a,4.8]

## 3.3 - Selected Total Synthesis of the Cylindricine Alkaloid

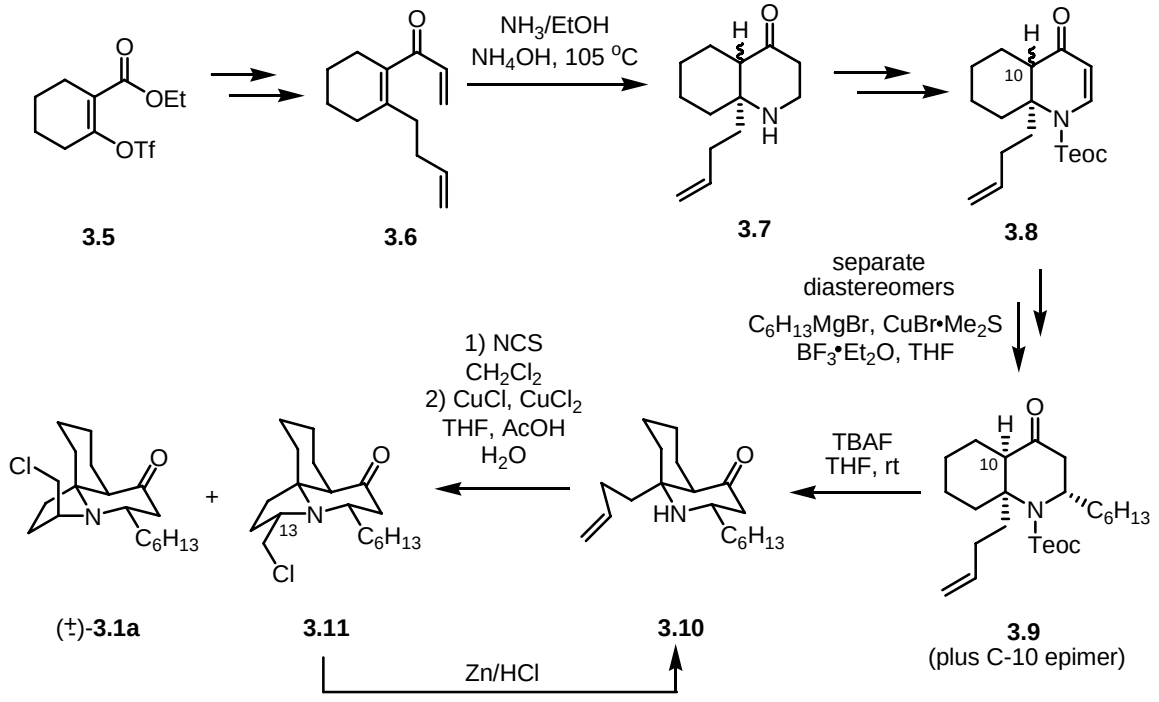
The unique structural motif of the cylindricine alkaloids has attracted an impressive array of synthetic efforts.[3.9] Highlights of selected total syntheses of these marine natural products are presented in this section.

688. (g) Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1205. (h) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337.

[3.8] (a) Raub, M. F.; Cardellina, II, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 3178. (b) Dutta, S.; Abe, H. Aoyagi, S.; Kibayashi, C.; Gates, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 15004.

[3.9] (a) For a review concerning total syntheses of the cylindricines, fasicularin and lepadiformine alkloids see: Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531. (b) For a review on the synthesis of cylindricines see: Liu, J.; Hsung, R. P. *Chemtracts* **2005**, *18*, 321.

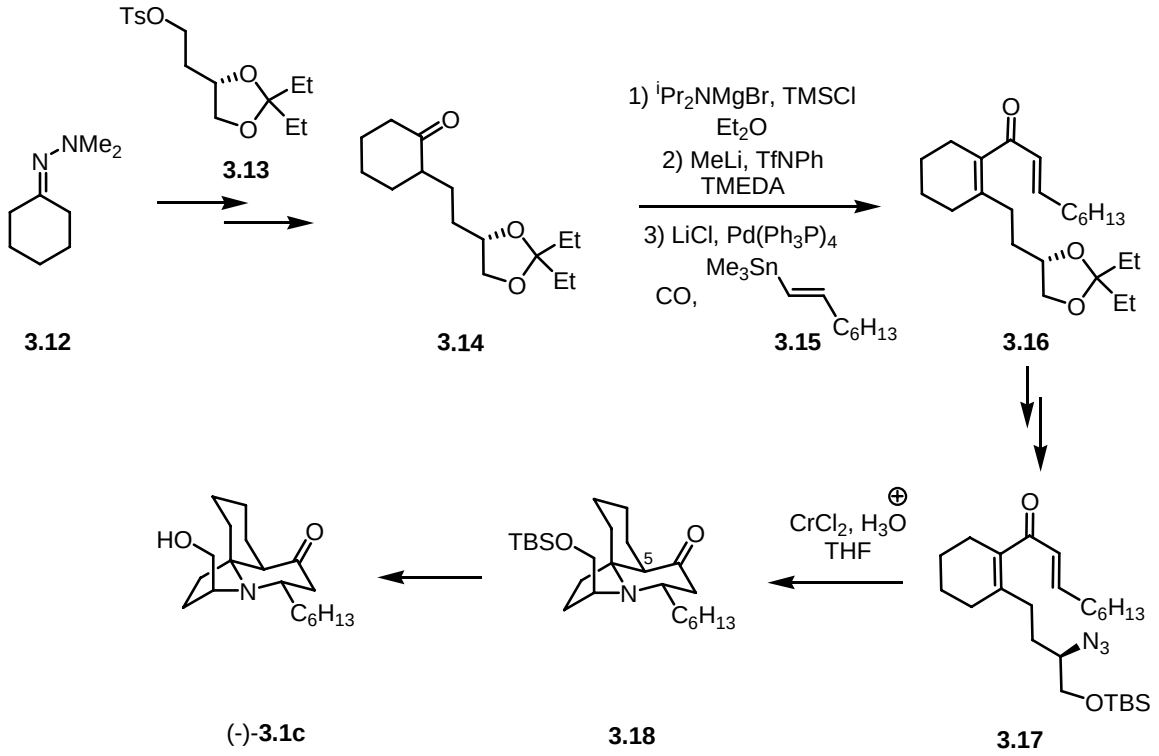
Heathcock and Liu reported a total synthesis of (±)-cylindricine A (**3.1a**) and B (**3.1b**)[3.10] that closely resembled a previous total synthesis of these compounds by Snider and Liu (Scheme 3.1).[3.11] One of the key steps in the Heathcock approach was a double Michael reaction of ammonia with dienone (**3.6**) to produce the 1-azadecalin (**3.7**) as a 1:1 *cis*:*trans* mixture. The latter was then converted to the vinylogous amides (**3.8**) and 10-*epi*-(**3.8**), which could be separated by HPLC. A highly stereoselective conjugate addition of hexyl Grignard to these vinylogous amides in the presence of $BF_3{\cdot}OEt_2$ and $CuBr{\cdot}Me_2S$ afforded ketones (**3.9**) and 9-*epi*-(**3.9**). Removal of the Teoc group with TBAF from both (**3.9**) and its *trans*-fused isomer convergently led to the more stable *cis*-azadecaline (**3.10**). The C-ring was then constructed by a nonstereoselective copper catalyzed *N*-chloroamine/olefin radical cyclization which afforded a mixture of racemic cylindricine A (**3.1a**) and the undesired C-13 epimer (**3.11**) in a 1:1 ratio. The latter could be recycled back to amino olefin (**3.10**) by zinc/HCl reduction.




**Scheme 3.1** Highlights of the Heathcock synthesis of (±)-cylindricine A (**3.1a**).

[3.10] Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263.
[3.11] Snider, B.; Liu; T. *J. Org. Chem.* **1997**, *62*, 5630.

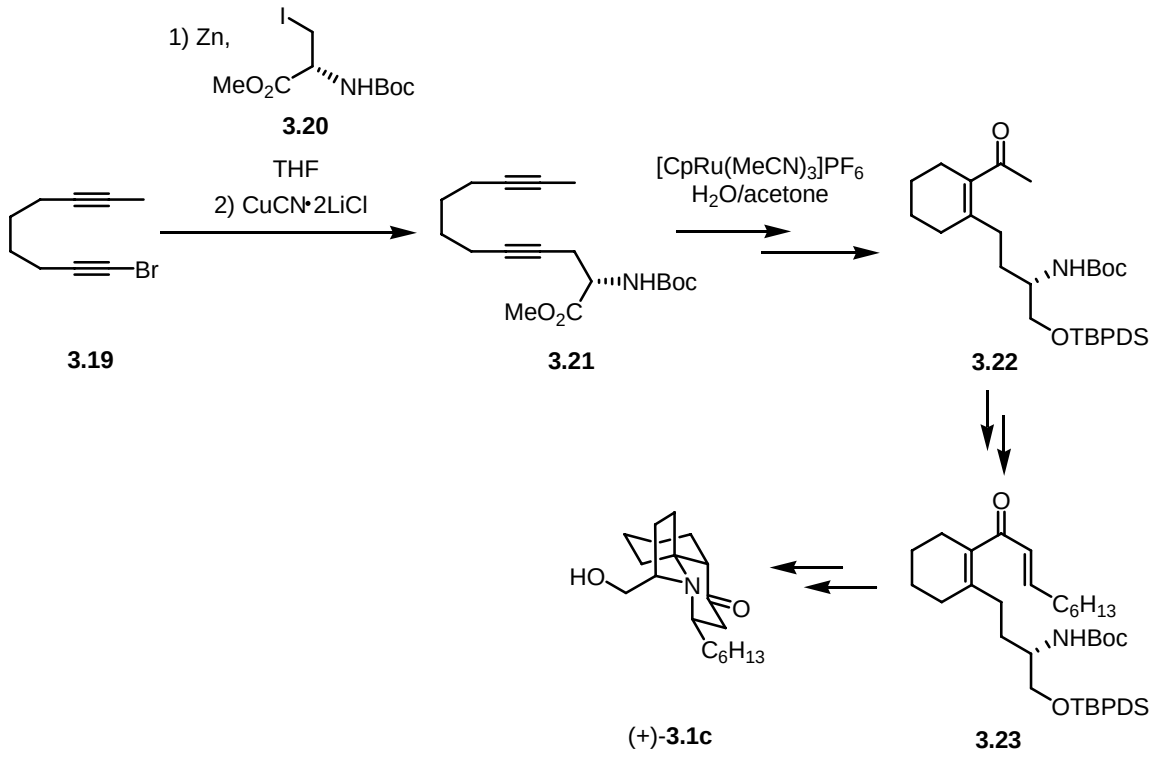
Molander and Rönn reported an enantioselective total synthesis of (-)-cylindricine C (**3.1c**) also based on a double Michel addition, but performed in an intramolecular manner (Scheme 3.2).[3.12] The chiral ketone (**3.14**), obtained from hydrazone (**3.12**) and the enantiomerically pure tosylate (**3.13**), was converted into dienone (**3.16**) *via* a sequence that included as the pivotal step a carbonylative Stille coupling with stananne (**3.15**). Ketal (**3.16**) was transformed into azide (**3.17**) by standard functional group transformations. Upon treatment with $CrCl_2$ under slightly acidic conditions, the latter afforded the TBS-protected cylindricine (**3.18**) *via* a tandem sequence that included the reduction of the azide (**3.17**) to the corresponding amine, a double Michael addition and *in situ* epimerization at C-5 to afford the thermodynamically more stable cylindricine system.




**Scheme 3.2** Highlights of the Molander synthesis of (-)-cylindricine C (**3.1c**).

[3.12] Molander, G. A.; Rönn, M. *J. Org. Chem.* **1999**, *64*, 5183.

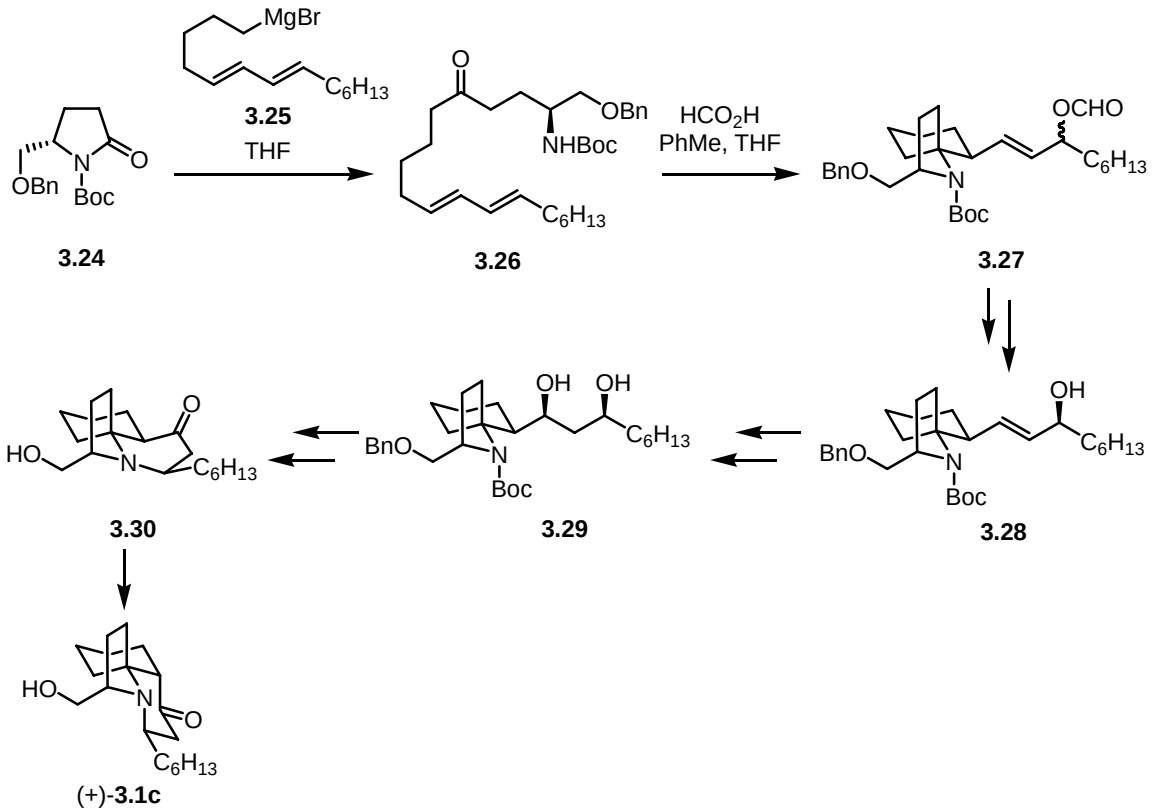
Trost and Rudd reported a total synthesis of (+)-cylindricines C (**3.1c**), D (**3.1d**) and E (**3.1e**) where an efficient ruthenium-catalyzed diyne cyclization was used to access the key amino dienone substrate that Molander and Rönn previously employed in their approach to these compounds (Scheme 3.3).[3.13] Using the methodology of Knochel, diyne (**3.19**) was coupled with enantiomerically pure iodide (**3.20**) to afford the ester (**3.21**). After some group manipulation involving the ester functionality, a chemoselective ruthenium-catalyzed hydrative cyclization was performed producing enone (**3.22**), which was then converted into dienone (**3.23**). The latter was converted into (+)-cylindricine (**3.1c**) using Molander's intramolecular Michael approach (*vide supra*, Scheme 3.2).




**Scheme 3.3** Highlights of the Trost synthesis of (+)-cylindricine C (**3.1c**).

[3.13] Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, 5, 4599.

Kibayashi and co-workers reported an approach to (+)-cylindricine C (**3.1c**) involving a *N*-acyliminium ion/diene cyclization cascade as the key step (Scheme 3.4).[3.14,3.15] Enantiomerically pure lactam (**3.24**) underwent addition with diene-Grignard (**3.25**) to produce ketone (**3.26**). Upon treatment with formic acid, the latter underwent a stereoselective cyclization affording spirocycle (**3.27**) as a mixture of stereoisomers which, after functional group manipulation, were convergently and stereoselectively converted into *β*-alcohol (**3.28**). Functional group manipulation, which included a hydroxyl-directed epoxidation, afforded the diol (**3.29**). The latter was then converted into tricyclic ketone (**3.30**) in a sequence that included as the key step an intramolecular displacement reaction. Base-promoted epimerization finally afforded (+)-cylindricine C (**3.1b**). Hsung and co-workers used a similar approach in theirs total synthesis of (+)-cylindricine C.[3.16]



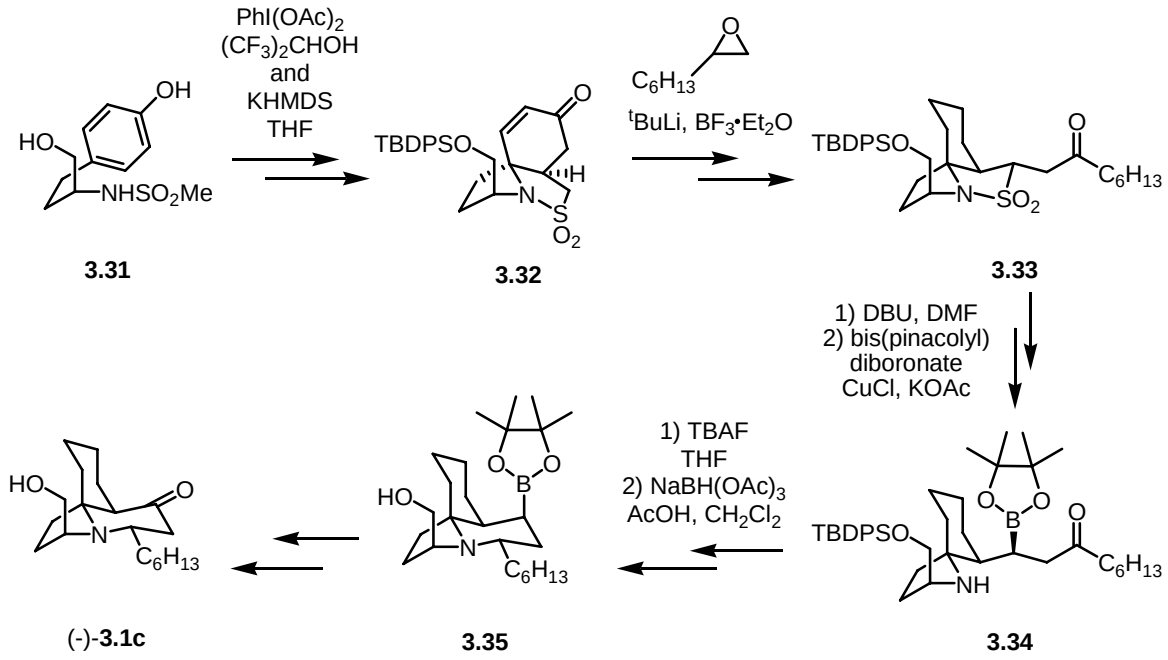

**Scheme 3.4** Highlights of the Kibayashi synthesis of (-)-cylindricine C (**3.1c**).

[3.14] Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473.

[3.15] For another approach to (+)-cyclindricines by the Kibayashi's group see: Arai, T.; Abe, Hideki, Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2004**, *45*, 5921.

[3.16] (a) Liu, J.; Swidorski, J. J.; Peters, S. D.; Hsung, R. P. *J. Org. Chem.* **2005**, *70*, 3898. (b) Liu, J.; Hsung, R. P.; Peters, S. D. *Org. Lett.* **2004**, *6*, 3989.

Ciufolini and co-workers prepared (-)-cylindricine C (**3.1c**) enantioselectively using a unique approach (Scheme 3.5).[3.17] The synthesis started with enantiomerically pure sulphonamide (**3.31**) which, upon oxidation with $PhI(OAc)_2$ and treatment with KHMDS, afforded adduct (**3.32**) in good selectivity (7:1 in favour of the latter). After complete reduction of the *α,β*-unsaturated system (not shown), the resulting sulphonamide was treated with $^tBuLi$ and the anion obtained was alkylated with 1-octene oxide. Subsequent Dess-Martin oxidation afforded ketone (**3.33**). Subjection of the latter to DBU resulted in an isolable *α,β*-unsaturated ketone (not shown) which was subjected to Miyaura borylation conditions delivering boronic ester (**3.34**) as a single stereoisomer. Removal of the silyl ether protecting group followed by an hydroxyl-directed reductive amination with $NaBH(OAc)_3$ delivered tricycle (**3.35**). Functional group manipulation, which included the oxidative conversion of the boronate to the alcohol, finally delivered (-)-cylindricine C (**3.1c**).



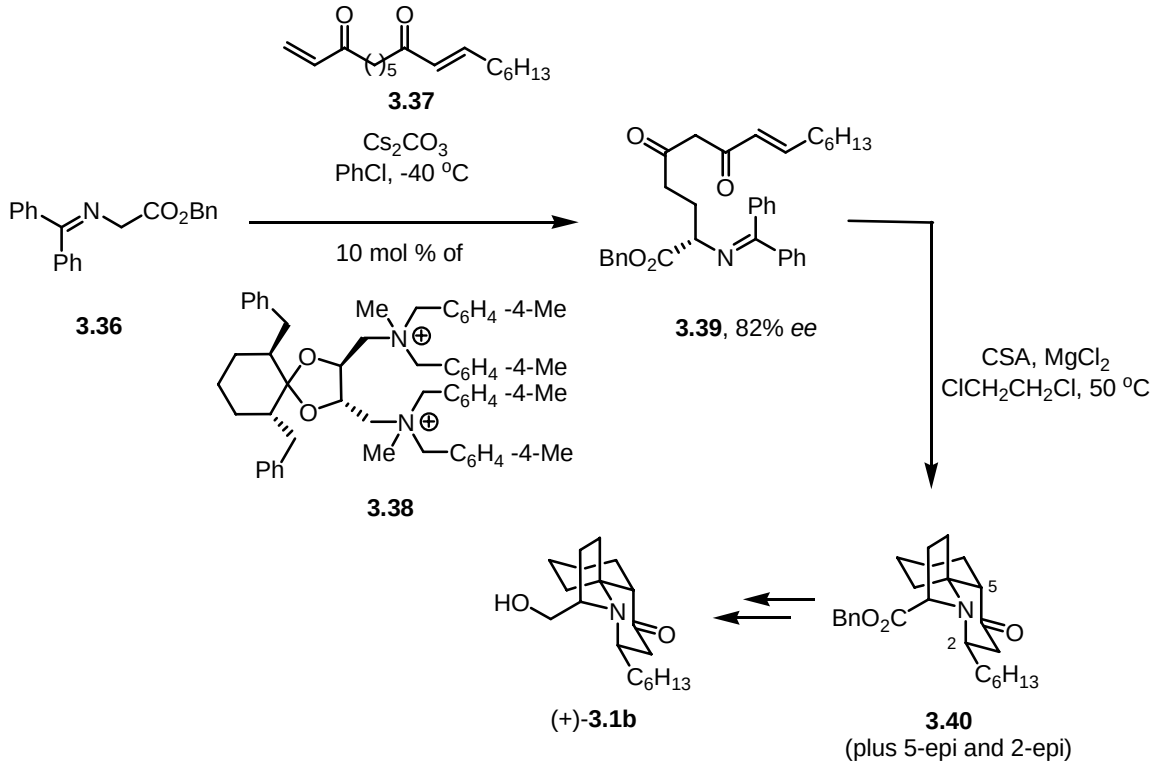

**Scheme 3.5** Highlights of the Ciufolini synthesis of (-)-cylindricine C (**3.1c**).

Recently, Shibasaki and co-workers reported a very short synthesis of (+)-cylindricine C (**3.1c**) using as the pivotal step the catalytic asymmetric Michael reaction of glycine Schiff base (**3.36**) to dienone (**3.37**) (Scheme 3.6).[3.18] In the presence of the newly

[3.17] Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336.

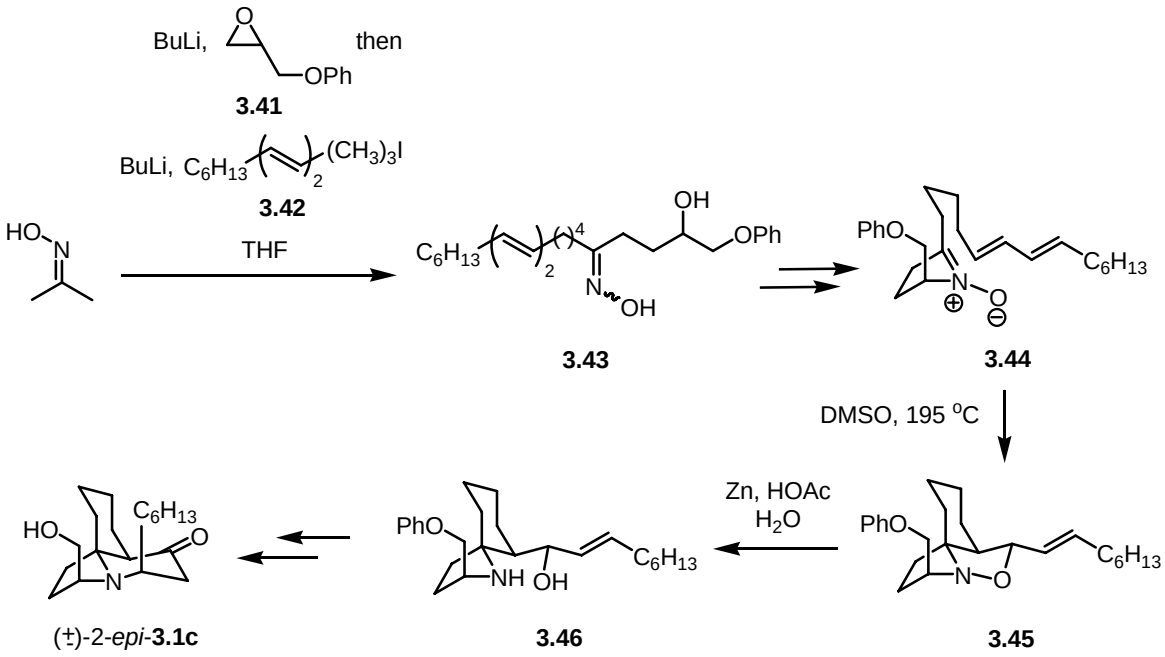
[3.18] Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakuraba, S.; Oshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4635.

developed two-center organocatalyst (**3.38**), the expected diketone (**3.39**) was obtained with fairly good enantiomeric excess (82%). Subsequent acid-promoted tandem cyclization using $MgCl_2$ as additive produced a mixture of the desired tricyclic amine (**3.40**) together with the C5- and C2-*epi* compounds in a 84:9:7 ratio, respectively. The former was then easily converted to (+)-cylindricine C (**3.1c**) by functional group manipulation.




**Scheme 3.6** Highlights of the Shibasaki synthesis of (+)-cylindricine C (**3.1c**).

In addition to the previous total syntheses of the cylindricines, several groups have reported interesting approaches to epimeric structures. A notorious example is Weinreb and co-workers' attempted total synthesis of (±)-cylindricine C (**3.1c**) by using an intramolecular nitrone-diene 1,3-dipolar cycloaddition as the key step (Scheme 3.7). The synthesis began with the sequential alkylations of acetone oxime with epoxide (**3.41**) and diene iodide (**3.42**) to afford oxime (**3.43**). Standard transformations converted the latter into nitrone (**3.44**) which upon heating underwent a cycloaddition to produce isoxazolidine (**3.45**). Reductive cleavage of the N-O bond, followed by a stereoselective tandem oxidation-Michael addition afforded the tricyclic core of 2-*epi*-cylindricine C, (±)-2-*epi*-(**3.1c**). However, all attempts made to converted the latter to the desired (±)-cylindricine C (**3.1c**) were unsuccessful.




**Scheme 3.7** Weinreb's synthesis of 2-*epi*-cylindricine C (**3.1c**).

# CHAPTER 4
# Molecular Mechanics Calculations

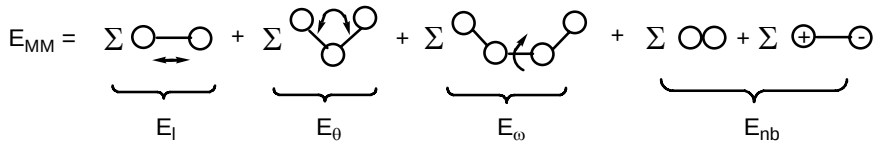
## 4.1 – Introduction[4.1]

Computational chemistry is among the most recent sub-disciplines of Chemistry to emerge and one of its fastest growing. In a nutshell, it involves developing computer software to solve chemical problems.

A class of problems which can be solved by computational chemistry concerns single molecule calculations. In principle any physical observable property of the molecule can be accessed. Depending on the property of interest and on the nature of the molecular system being studied, the calculations can be performed either with molecular mechanics (MM), *ab initio* or semi-empirical methods. Arguably, the latter two, being quantum mechanical-based, can offer a fairly rigorous description of the molecule from both a structural and electronic point of view. They can, however, be prohibitive in terms of both time and computer memory. MM, on the other hand, by taking an alternative approach to the Born-Oppenheimer approximation, in that the electronic distribution associated with each atom is fixed and only nuclear motion is considered, allows much larger chemical systems to be investigated in considerably shorter times.

In MM a molecule is represented as a collection of spheres joined by springs. The motions of the atoms are described by the laws of classical physics and simple potential energy functions are used. The molecular mechanics energy of a molecule, $E_{MM}$, is then calculated as a sum of the bonding and non-bonding interactions present. Each bond length, angle and dihedral is considered individually and non-bonded interactions account for the influence of non-covalent forces (*e.g.*, van der Waals and Coulombic) (Equation 4.1).

[4.1] (a) Cramer, J. C. in "Essentials of Computational Chemistry" **2003**, Wiley, Chichester. (b) Jensen, F. in "Introduction to Computational Chemistry" **2003**, Wiley, Chichester. (c) Hinchliffe, A. in "Molecular Modelling for Beginners" **2003**, Wiley, Chichester. (d) Goodman, J. M. in "Chemical Applications of Molecular Modelling" **1998**, The Royal Society of Chemistry, Cambridge. (e) Grant, G. H.; Richards, W. G. in "Computational Chemistry" **2004**, *29*, Oxford University Press, Oxford Chemistry Primers, Oxford.




(**Equation 4.1**)

where $E_l$, $E_\theta$, $E_\omega$ and $E_{nb}$ are, respectively, the total bond, angle, dihedral and non-bonded energies.

A molecular property which is usually of major interest to organic chemists is conformation.[4.2] MM allows performing conformational searches so that all the possible conformations of a molecule and respective energies are obtained.[4.3] The population ratios between the different conformations can then be calculated by using the Boltzmann equation (Equation 3.2).

$$\text{Boltzmann factor} = \exp\left(\frac{-\Delta E_{MM}}{RT}\right) \qquad \textbf{Equation 4.2}$$

where $\Delta E_{MM}$ ($Jmol^{-1}$) is the difference in energy between two conformations, R is the gas constant (8.314 $JK^{-1}mol^{-1}$) and T (K) is the absolute temperature.

Although a powerful tool, it is important to keep in mind the caveats of MM. One of the main limitations of MM concerns its parameterized nature, *i.e.*, the results accuracy is dependent of the "quality" of the force field employed, *i.e.*, the set of parameters (*e.g.*, force constants, bond lengths, etc) and potential functions used. A second limitation of MM is that, by neglecting explicit representation of electrons, it can not, strictly speaking, be used to discuss transition states (TS) of processes where bonds are being made and/or broken.

The latter limitation can, to some extent, be overcome by considering certain approximations. A TS is a minimum energy structure with respect to all but one degree of freedom, the reaction coordinate. Constraining the latter still leaves 3N-7 degrees of freedom unchanged which, for large systems, usually account for most of the properties of the system. This argument provides the basis for one of the MM approaches to TS modeling , which consists in treating the TS as normal ground state (Figure 4.1).[4.4]

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[4.2] Eliel, E. L.; Wilen, S. H. in "Stereochemistry of Organic Compounds" **1994**, Wiley, New York.
[4.3] Lipkowitz, K.; Peterson, M. *Chem. Rev.* **1993**, *93*, 2463.
[4.4] Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439.

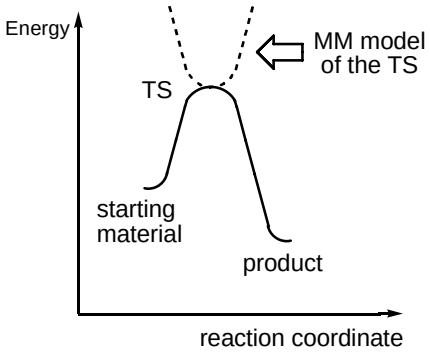



**Figure 4.1** MM approach to TS.

Several approaches have been used to model TS using empirical force fields. The crudest one involves estimating a value for the reaction coordinate and using it to model the TS using an energy-minimized structure of the reactants or the products.[4.5] Since theoretical calculations have shown that geometrical parameters in TS structures have a relatively narrow range of values for a given type of reaction, this expedite assumption is not as a drastic as it might seem. In more sophisticated approaches, a combination of *ab initio* methods and MM is employed: quantum mechanics is used to treat the atoms involved in the bond-making/breaking processes whereas all the remaining atoms are considered using empirical force fields.

Finally it is noted that MM works best when similar systems, *e.g.*, epimers or diastereomeric TS, are being compared. In such cases, many of the errors in the force field tend to cancel and the differences in energy that are calculated are likely to be fairly reliable.

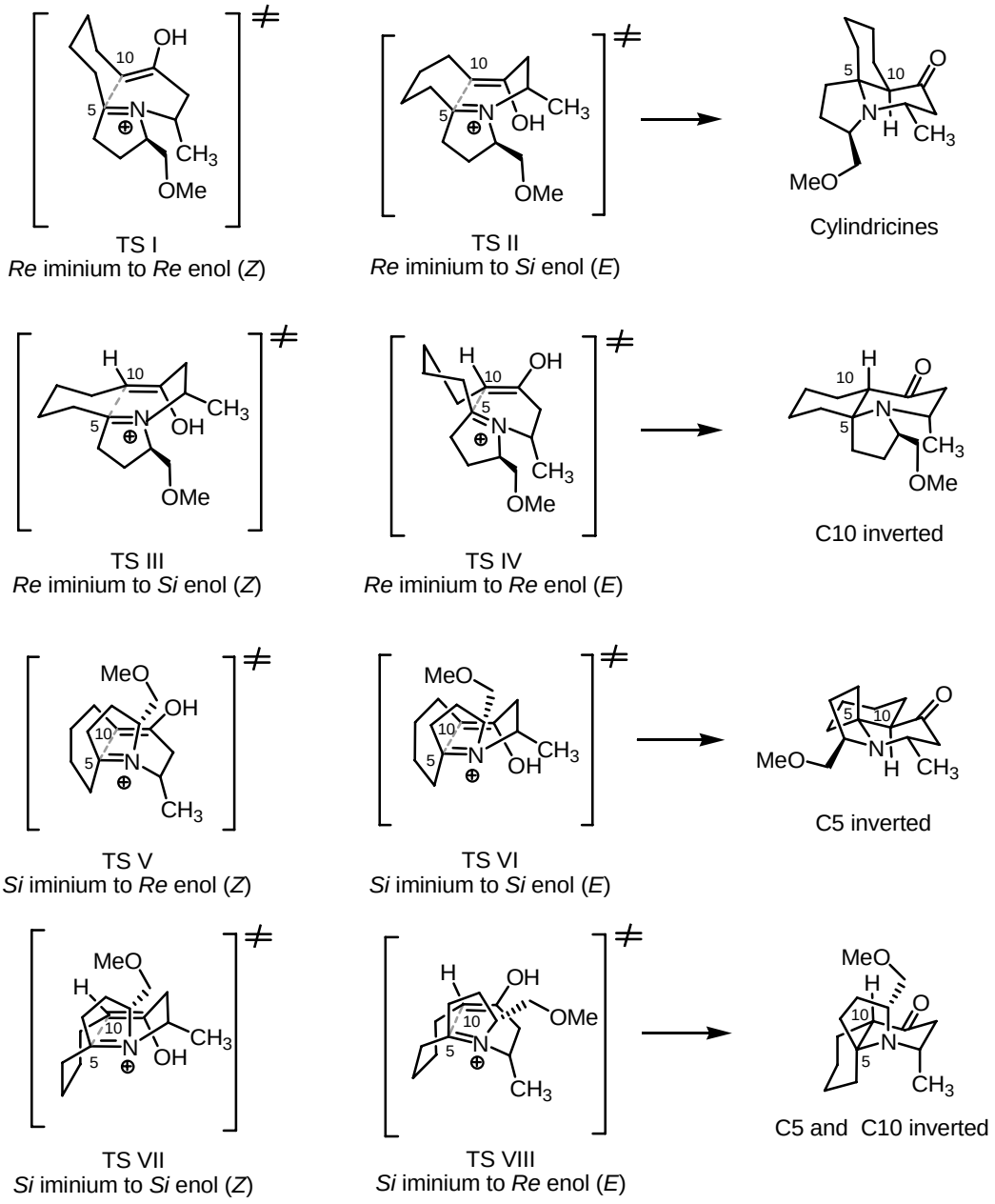
[4.5] For selected examples see: (a) Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1979**, 3303. (b) Shea, K. J.; Stoddard, G. J.; England, W. P.; Haffner, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 2635.

## 4.2 – Results and Discussion

The MM TS for the proposed transannular Mannich (TAM) reaction (*vide* Chapter 2) were accessed and quantified using the following approach. Conformational searches were first performed on energy-minimized structures of the two possible starting materials, the macrocyclic iminium *E*- and *Z*- enols. For each isomer a set of different conformers and their respective energy, $E_{MM}$, were obtained, which allowed calculating the respective conformer ratio. Then, and in order to crudely model the TS, the C5–C10 distance in each of the conformers previously found was constrained. Because the reactants are being used to access the TS, the reaction coordinate takes the reagents→TS sense. Therefore, the C5–C10 distance was decreased since it corresponds to the bond being formed. The constrained energies found, $E_{MMc}$, are assumed to be the TS energies corresponding to the Mannich reaction of each conformer and were then used to obtain the product distribution. An identical procedure, *mutatis mutandis*, was then applied to the possible reaction products, the cylindricines and their three C-5 and C-10 diastereomers (*vide infra*, Scheme 4.1). In these cases, because the reaction coordinate takes the products→TS sense, the C5–C10 was increased.

All the calculations were performed in Macromodel using MMFF as the force field and in vacuum. The initial energy minimization of the different structures was performed using TNCG and a maximum of 500 iterations. The structures thus obtained were then subjected to a conformational search using SUMM. Since 9 free torsions were found for the iminium-enols *E* and *Z* (to which corresponds $3^9 = 19683 \sim 20000$ possible rotations), 20000 steps were used. Only conformers within 20 $kJmol^{-1}$ from the least energetic conformation found were considered. The distance C5–C10 was constrained to 2Å, with a force constant of 5000 $kJmol^{-1}Å^{-2}$. For convenience, the calculations were performed using a methyl group at C-2.

Since the intramolecular Mannich reaction can take place between the two faces of the iminium ion and the two faces of each enol isomer, there are four possible diastereomeric products (Scheme 4.1).



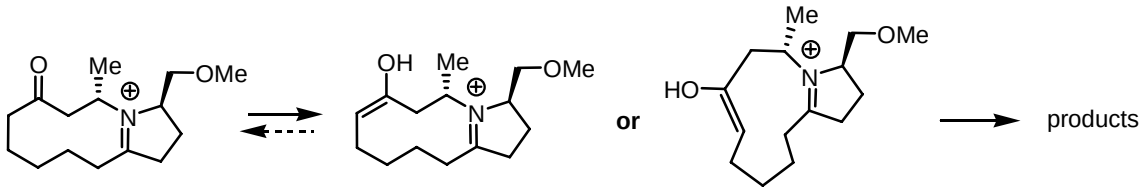

**Scheme 4.1** Possible products of the TAM reaction and respective TS.

The MM TS corresponding to the various possible Mannich reactions were first accessed using the reactants as models (Table 4.1).

**Table 4.1** MM calculations for iminium *Z*- and *E*-enols.

| | Conformer | $E_{MM}$ (kJmol$^{-1}$) | $N_1/N_x$ (300 K) | $E_{MMc}$ (kJmol$^{-1}$) | TS type | Product Formed | Product Distribution (%) |
|---|---|---|---|---|---|---|---|
| | **Iminium Z-enol** | | | | | | |
| | 1 | 198.8 | 1 | 551.4 | III | C10 inverted | 0.02 |
| | 2 | 203.2 | 5.9 | 575.3 | III | C10 inverted | - |
| | 3 | 212.6 | 255.4 | 559.6 | III | C10 inverted | - |
| | 4 | 215.4 | 786.7 | 545.3 | VII | C5 and C10 inverted | 0.23 |
| | 5 | 215.5 | 811.5 | 587.3 | V | C5 inverted | - |
| | 6 | 216.7 | 1326.0 | 539.8 | I | Cylindricine | 2.07 |
| | 7 | 217.7 | 1994.8 | 583.9 | III | C10 inverted | - |
| ⇨ | 8 | 218.7 | 3293.5 | 530.2 | VII | C5 and C10 inverted | 97.68 |
| | **Iminium *E*-enol** | | | | | | |
| | 1 | 188.1 | 1 | 577.7 | VIII | C5 and C10 inverted | 0.02 |
| ⇨ | 2 | 190.5 | 2.7 | 556.7 | II | Cylindricine | 87.47 |
| | 3 | 191.5 | 4.0 | 577.7 | VIII | C5 and C10 inverted | 0.02 |
| | 4 | 203.2 | 422.2 | 583.2 | VIII | C5 and C10 inverted | - |
| | 5 | 204.5 | 738.1 | 583.2 | VIII | C5 and C10 inverted | - |
| | 6 | 205.4 | 1021.2 | 568.9 | II | Cylindricine | 0.65 |
| | 7 | 206.2 | 1445.2 | 601.3 | VI | C5 inverted | - |
| | 8 | 206.3 | 1469.8 | 561.7 | II | Cylindricine | 11.58 |
| | 9 | 206.4 | 1537.4 | 573.0 | VIII | C5 and C10 inverted | 0.13 |
| | 10 | 206.9 | 1876.6 | 619.4 | VI | C5 inverted | - |
| | 11 | 207.9 | 2803.0 | 573.0 | VIII | C5 and C10 inverted | 0.13 |

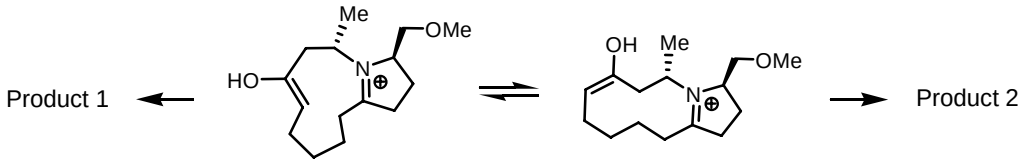
The first scenario that is possible to consider from this data corresponds to the situation where the macrocyclic iminium ion affords exclusively only one of the iminum enol isomers (Scheme 4.2). The population distributions calculated for each iminium enol isomer for this case are shown in the respective sub-tables of Table 4.1.



**Scheme 4.2**

As it can be seen each iminium enol is predicted to react very differently in the Mannich step of the TAM reaction: whereas the iminium *E*-enol is expected to afford the desired cylindricines almost exclusively (mainly *via* its conformers 2 and 8), the iminium *Z*-enol is predicted to produce mainly the diastereoisomer with the opposite configuration at C-5 and C-10 (mostly through its conformer 8). Intuitively, however, this is an unlikely scenario as the energy barriers corresponding to the formation of the two iminium enols are expected to be comparable.

A more likely situation is shown in Scheme 4.3 and it considers the possibility that the two iminium enols are both present in the reaction mixture. These two isomers are assumed to interconvert and to react by first-order kinetics to give a different product.




**Scheme 4.3**

Two limiting cases can be considered for this scenario.

On one hand, it is possible to envision the energy barrier for the interconversion of the two iminium enol intermediates being significantly higher than the energy barriers for the subsequent Mannich reaction ("anti Curtin-Hammett conditions"). In such case, the product ratio of the overall TAM reaction should reflect the relative energies of the iminium enol intermediates (Figure 4.2). Such a scenario is conceivable since, as result of the intrinsic limitations of MM to deal with TS, the high TS energies calculated are likely to be largely overestimated. This overestimation occurs because interactions which are considered by MM as fully non-bonding and repulsive will be partially bonding in the real TS. Assuming that the relative order of the calculated TS energies with respect to each conformer is correctly predicted, then the iminium *E*-enol will react preferentially through its conformer 2 to deliver the cylindricines, whereas the reaction of the iminium Z-enol will proceed mainly *via* conformer 8 to afford the diastereomer with inverted C-5 and C-10 configuration. Since the energy of the former is significantly lower than the latter (190.5 kJmol$^{-1}$ *versus* 218.7 kJ mol$^{-1}$), and because these intermediates should be representative of the TS for the Mannich reaction (Hammond postulate), the cylindricines are expected be the main/exclusive product of the TAM reaction.

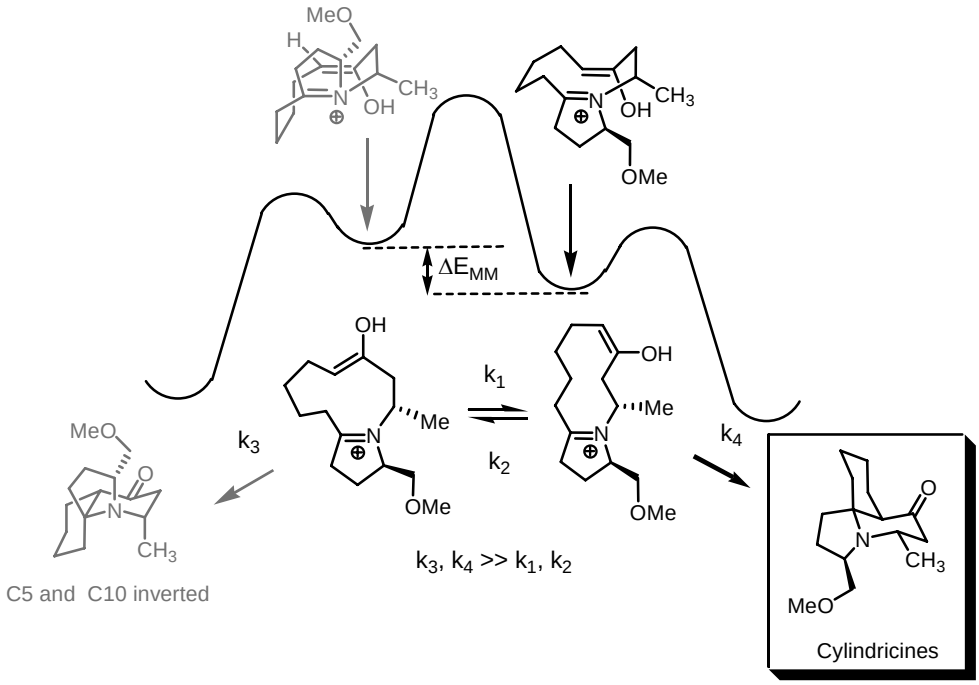



**Figure 4.2** Mannich step in the TAM reaction under "anti Curtin-Hammett" conditions.

On the other hand, it is possible that the Mannich reaction proceeds under Curtin-Hammett conditions, in which case the product distribution will be determined by the transition state energies (Figure 4.3). The lowest TS found for the iminium *Z*-enol is predicted to produce the diastereoisomer with inverted configuration at C-5 and C-10 whereas the lowest TS for the iminium *E*-enol is expected to deliver the desired cylindricines. Considering that the former is significantly lower in energy than the latter ($E_{MMc}$ of 530.2 kJmol$^{-1}$ *vs.* 556.7 kJmol$^{-1}$, respectively), the undesired diastereomer is anticipated to be the main/exclusive product of the TAM reaction.

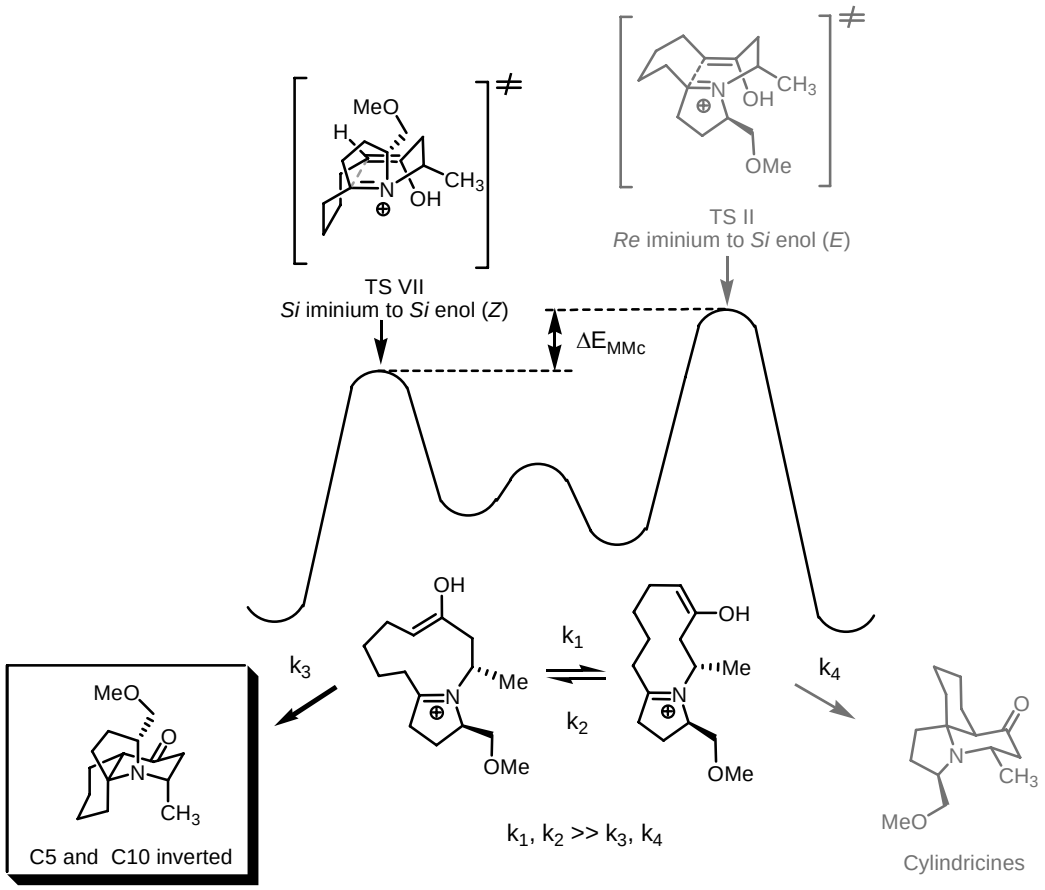



**Figure 4.3** The Mannich step in the TAM under Curtin-Hammett conditions.

Unlike the previous "anti-Curtin-Hammett" case where the calculations were based on ground state energies, the current predictions are based on TS energies, for which MM is far less trustworthy. It is thus conceivable that, in reality, the lowest TS leading to the cylindricines is lower that the lowest TS leading to the undesired diastereomer. Therefore, the product distribution predicted under Curtin-Hammett conditions, where the undesired diastereomer is the main product, should either be disregarded all together or reluctantly accepted.

It is important to stress that the previous predictions correspond to two limit scenarios. An intermediate situation where the energy barriers for the interconversion of the iminium enols and the Mannich reaction are comparable can not *a priori* be excluded. The experimental product ratio is thus necessary to clarify which particular case in operating.

The MM TS were also accessed using the products as models (Table 4.2).

**Table 4.2** MM calculations for products.

| Conformer | $E_{MM}$ ($kJmol^{-1}$) | $N_1/N_x$ (300 K) | $E_{MMc}$ ($kJmol^{-1}$) |
|---|---|---|---|
| Cylindricines | | | |
| 1 | 192.5 | 1 | 162.1 |
| 2 | 193.0 | 1.2 | 170.3 |
| 3 | 196.5 | 5.0 | 174.5 |
| 4 | 200.2 | 22.0 | 177.7 |
| 5 | 200.2 | 22.0 | 170.0 |
| 6 | 202.5 | 54.8 | 190.5 |
| 7 | 203.7 | 89.2 | 174.0 |
| 8 | 204.4 | 117.9 | 181.9 |
| 9 | 204.6 | 129.3 | 182.8 |
| 10 | 205.0 | 151.0 | 174.8 |
| 11 | 205.2 | 161.1 | 174.1 |
| 12 | 205.2 | 162.0 | 183.4 |
| 13 | 205.8 | 206.7 | 175.3 |
| 14 | 207.8 | 465.8 | 179.6 |
| 15 | 207.8 | 468.0 | 196.0 |
| 16 | 209.0 | 756.4 | 179.6 |
| 17 | 210.4 | 1313.6 | 190.5 |
| 18 | 212.2 | 2687.6 | 181.2 |
| C-10 inverted | | | |
| 1 | 200.3 | 1 | 183.9 |
| 2 | 207.3 | 16.4 | 191.0 |
| 3 | 212.4 | 127.1 | 195.8 |
| 4 | 213.3 | 183.3 | 196.7 |
| 5 | 213.3 | 183.4 | 197.1 |
| 6 | 215.6 | 456.2 | 193.4 |
| C-5 inverted | | | |
| 1 | 220.0 | 1 | 202.9 |
| 2 | 221.6 | 1.9 | 204.6 |
| 3 | 224.3 | 5.5 | 204.6 |
| 4 | 226.0 | 10.8 | 208.8 |
| 5 | 226.5 | 13.2 | 218.7 |
| 6 | 229.2 | 39.5 | 212.7 |
| 7 | 229.2 | 39.8 | 212.8 |
| 8 | 231.1 | 85.1 | 224.0 |
| 9 | 232.8 | 164.2 | 225.2 |
| 10 | 235.0 | 408.2 | 217.2 |
| 11 | 239.0 | 1988.1 | 231.7 |

**Table 4.2** (cont.) MM calculations for products.

| Conformer | $E_{MM}$ (kJmol$^{-1}$) | $N_1/N_x$ (300 K) | $E_{MMc}$ (kJmol$^{-1}$) |
|---|---|---|---|
| C-5 and C-10 inverted | | | |
| 1 | 194.4 | 1 | 171.5 |
| 2 | 197.0 | 2.8 | 175.3 |
| 3 | 198.6 | 5.4 | 177.5 |
| 4 | 201.6 | 17.8 | 179.7 |
| 5 | 203.3 | 36.5 | 190.6 |
| 6 | 204.1 | 48.8 | 182.8 |
| 7 | 205.5 | 84.9 | 192.7 |
| 8 | 209.2 | 384.8 | 183.4 |
| 9 | 210.0 | 533.1 | 197.2 |
| 10 | 210.8 | 711.6 | 183.7 |
| 11 | 211.1 | 809.1 | 184.5 |
| 12 | 211.5 | 950.8 | 188.2 |
| 13 | 211.6 | 981.1 | 198.5 |
| 14 | 212.6 | 1498.4 | 199.6 |
| 15 | 212.7 | 1573.4 | 189.5 |
| 16 | 213.1 | 1807.6 | 187.5 |
| 17 | 213.6 | 2212.4 | 196.4 |
| 18 | 213.7 | 2349.4 | 201.4 |

The first point worth mentioning in these results is that the TS energies obtained are lower than the energy of the corresponding unconstrained conformers! This is a limitation of the force field used, since the energy of the C5–C10 bond being constrained (*i.e.*, elongated) is not being considered for the calculation of the $E_{MMc}$. However since this is systematic in this set of calculations, it is still possible to compare the obtained TS energies.

Based on the above results, the products distribution can be calculated (Table 4.3).

**Table 4.3**

| Diastereoisomer | $E_{MM}$ Product Distribution (%) (300 K) | $E_{MMc}$ Product Distribution (%) (300 K) |
|---|---|---|
| Cylindricine | 66.2 | 97.7 |
| C10 inverted | 2.9 | - |
| C5 inverted | - | - |
| C10 and C5 inverted | 30.9 | 2.3 |

In contrast with what was observed previously when the TS was modeled based on iminium enols reactancts, for the present case the lowest energy conformer of each set has the lowest energy TS. This is likely to be a consequence of the similar bond organization in the TS and in the rigid tricyclic structure of the products as opposed to the more flexible iminium enols. In this sense, it could be argue that the products should be a better model for the TS (*i.e.*, a late TS), which may reinforce the present results in detriment of those obtained when the iminum enols were studied.

According to the results on Table 4.3 the desired cylindricines are predicted to be obtained with moderate to good selectivity with respect to the diastereomer with inverted configuration at C-5 and C-10, depending on which set of energies is used in the calculations. For the reasons mentioned before, the more optimistic results obtained when the TS energies are used should be approach with more scepticism.

An important corollary of the above results is that since the cylindricine skeleton has a lower energy than any of the possible byproducts, if the TAM could be performed under thermodynamic control, then the desired cylindricines could be obtained with some selectivity.

## 4.3 - Conclusion

The Mannich step in the planned TAM reaction was investigated using MM. In particular, MM was used to access the lowest energy conformers of the reactants, iminium *E*- and *Z*-enols, and of the products, cylindricines and the possible C-5 and C-10 diastereomers, and to crudely model the TS of the Mannich reaction.

In should be emphasized that as result of the intrinsic limitations of MM in dealing with TS, all the results obtained should be approach with a healthy dose of scepticism. This is particularly true for the present case where the reaction coordinate was defined in terms of a single distance, for which a somewhat arbitrary value of 2Å was used.

In the most reliable scenarios, where the energies of ground state species (*i.e.*, intermediates or products) were used to access the product ratio, the desired cylindricines are predicted to be the main product of the reaction. This was both the case when the iminium enols were used as a model for the TS and “anti Curtin-Hammett” conditions were assumed and when the TS was modelled after the products. Moderate to excellent selectivities in favour of the desired cylindricines

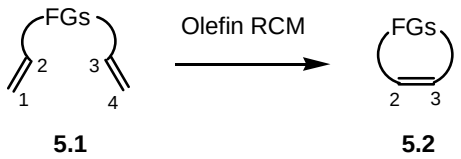
were predicted for these cases. On the other hand, when a Curtin-Hammett scenario for the Mannich reaction is assumed, the undesired diastereomer with inverted configuration at C-5 and C-10 is expected to be the main/exclusive product. Fortunately, it can be argue that this prediction is less trustworthy as it is based on MM TS energies. Hence, there is reason to be moderately optimistic that the TAM will afford the desired cylindricines as the main product.

More reliable results could have been obtained by constraining more than one degree of freedom in the system and/or by using a higher level method for the calculations such as *ab initio*.

# CHAPTER 5
# Results and Discussion

## 5.1 - Studies Towards Macrocycle (2.12) Based on a RCM Reaction

The metathesis reaction has recently established itself as extremely powerful tools in organic synthesis. The olefin ring-closing metathesis (RCM) in particular has emerged as a value method for ring formation.[5.1,5.2] This reaction involves the conversion of an (acyclic) diene (**5.1**) into the corresponding cyclic alkene (**5.2**) under the action of a metal carbene species (Figure 5.1).




**5.1** **5.2**

**Figure 5.1** Olefin RCM reaction.

One of the most important applications of RCM in organic synthesis has been in macrocyclizations reactions.[5.3] This RCM-based macrocylization approach is particularly important in those cases where the *E*/*Z* selectivity of the process, often one of RCM main limitations, is of no consequence, as for example when the resulting alkene system is to be hydrogenated.

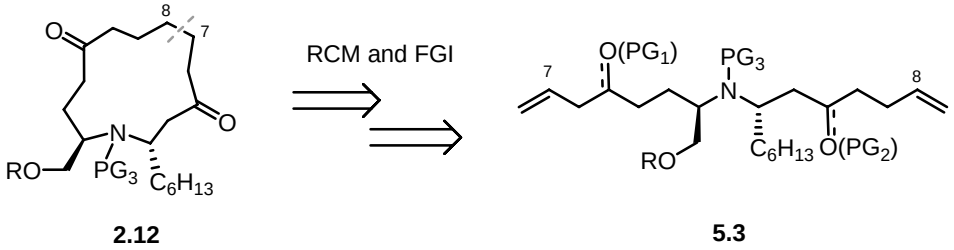
---

[5.1] For reviews see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Fürstner, A. *Top. in Cat.* **1998**, *4*, 285. (c) Hoveyda, A. H. *Top. Organomet. Chem.* **1998**, *1*, 105. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (e) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239.

[5.2] Soufflet, J.-P.; Commereuc, D.; Chauvin, Y. *Compt. Rend.* **1973**, *276*, 169.

[5.3] For selected examples see: (a) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 166. (b) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073. (c) Schinzer, D.; A. Bauer, A.; Böhm, O. M.; Limberg, A.; Cordes, M. *Chem. Eur. J.* **1999**, *5*, 2483. (d) Prunet, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 2826. (e) Maleczka Jr., R. E.; Terrell, L. R.; Geng, F.; Ward III, J. S. *Org. Lett.* **2002**, *4*, 2841. (f) Fürstner, A.; Jeanjean, F.; Razon, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 2097. (g) Barluenga, S.; Lopez, P.; Moulin, E.; Winssinger, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 3467.

Based on these considerations, diene (**5.3**) emerged as a suitable precursor to access the key macrocycle intermediate (**2.12**) (Scheme 5.1).

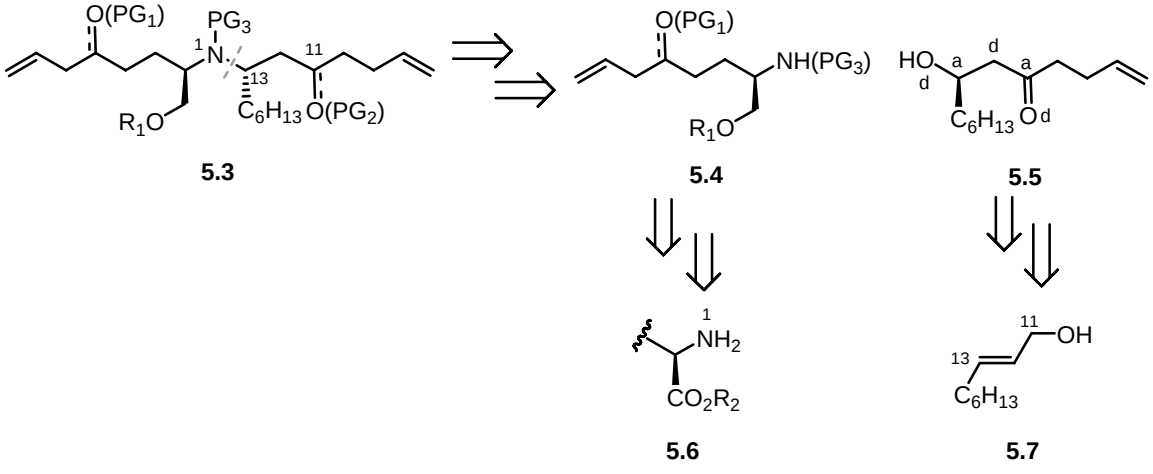



**Scheme 5.1** The RCM approach towards key macrocycle (**2.12**).

## 5.1.1 Synthetic Studies Towards Diene (5.3) *via* a Displacement Reaction

### 5.1.1.1 Retrosynthetic Considerations

The first strategy considered to access diene (**5.3**) explored the use of a $S_N2$-type displacement reaction to combine (activated) amine (**5.4**) with alcohol (**5.5**) (Scheme 5.2). The sense of disconnection shown would in principle allow the preparation of amine (**5.4**) from an *α*-amino acid (**5.6**) precursor. Alcohol (**5.5**) was planned to be access from allylic alcohol (**5.7**) with the required chirality being established by means of the Sharpless asymmetric epoxidation (SAE) reaction. Hence, the chirality of amine (**5.4**) would be derived from the chiral pool while that of alcohol (**5.5**) would be established by means of catalytic asymmetric synthesis.




**Scheme 5.2** Simplified retrosynthetic analysis for diene (**5.3**) based on a displacement reaction.

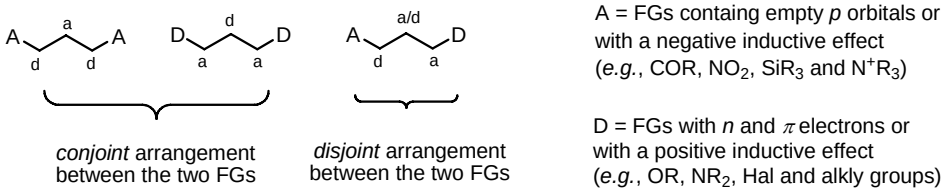
Secondary alcohols such as (**5.5**) can be poor substrates in $S_N2$-type displacement reactions with (activated) amines such as (**5.4**); however, it was argued that the 1,3-conjoint electronic arrangement[5.4] between the carbonyl and the hydroxyl functionalities in (**5.5**) would facilitate the coupling process between these two building blocks.[5.5]

### 5.1.1.2 Preparation of the Building Blocks Pertaining to the Displacement Approach

For convenience, the initial studies were performed in the racemic series.

The synthesis of *rac*-(**5.5**) began with the HWE reaction[5.6] of heptaldehyde with ethylphosphonate in an aqueous solution of $K_2CO_3$ to afford the desired (*E*)-*α,β*-unsaturated ethyl ester in a stereoselective manner and in high yield (95%).[5.7,5.8] DIBAL reduction of the latter proceeded in good yield (79%) delivering known allylic alcohol (**5.8**), which was then subjected to MCPBA epoxidation to produce the corresponding epoxyalcohol in 95% yield. Following the procedure of Kitching and co-workers,[5.9] treatment of the latter with Red-Al, afforded diol (**5.9**) in 77% yield,

[5.4] Functional groups, by virtue of their heteroatoms, modify the electronic properties of the adjacent hydrocarbon backbone. According to Ho,[5.5] two situations are possible: either the alternating polarity pattern along a chain of atoms created by each of the functional groups (FGs) reinforce or oppose each other, corresponding to a *conjoint* or a *disjoint* electronic arrangement, respectively (**Scheme 5.A**).




**Scheme 5.A** Conjoint and disjoint electronic arrangements between FGs.

[5.5] Ho, T.-L. in "Polarity Control for Synthesis" **1990**, Wiley, Illinois.
[5.6] For general references see: (a) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. (b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *62*, 1733. For a review see (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1988**, *89*, 863.
[5.7] Seguineau, P.; Villieras, J. *Tetrahedron Lett.* **1988**, *29*, 477.
[5.8] For an alternative procedure for the preparation of allylic alcohol (**5.8**), based on the stereoselective reduction of 2-nonyn-1-ol with $LiAH_4$ see ref. 5.9.
[5.9] Kitching W.; Lewis, J. A.; Perkins, M. V.; Drew, R.; Moore, C. J.; Schurig, V.; König, W. A.; Francke, W. *J. Org. Chem.* **1989**, *54*, 3893.

presumably *via* an internal hydride delivery.[5.10] After conversion of the 1,3-diol (**5.9**) to the *O*,*O*-benzylidene acetal (**5.10**),[5.11] accomplished in good yield (75%) by reaction of the former with benzaldehyde in the presence of a catalytic amount of $H_2SO_4$, a regioselective reductive opening of the latter with DIBAL afforded the primary alcohol (**5.11**) in 98% yield.[5.12] A subsequent Dess-Martin oxidation delivered the corresponding aldehyde which, without further purification, was reacted with the Grignard reagent (**5.12**)[5.13] producing the alcohol (**5.13**) in good yield (79%). Treatment of the latter with Dess-Martin periodinate (DMP) delivered ketone (**5.14**) in excellent yield (97%) yield (Scheme 5.3).

All that remained doing to prepare alcohol *rac*-(**5.5**) was to cleave the Bn protecting group from (**5.14**). Due to the C=C double bond in the latter, hydrogenolysis conditions, arguably the most commonly used method to convert benzylic ether into the corresponding alcohols,[5.14] were excluded. Therefore, we concentrated in deprotection methods based on the so-called "push and pull principle", namely the use of $BF_3{\cdot}Et_2O$-$SMe_2$[5.15a], $BBrMe_2$[5.15b] and $AlCl_3$-*N,N*-dimethyaniline.[5.15c] Unfortunately, all attempts to accomplish the removal of the Bn group from (**5.14**) using these conditions, led to failure as either extensive decomposition of the starting material was observed or complex mixtures were obtained. Interestingly, when ketone (**5.14**) was treated with $SMe_2$ in the presence $BF_3{\cdot}Et_2O$, the $^1$H-NMR of the crude product suggested that the sulfonium salt (**5.15**) was formed. The observation that only the (*E*)-*α,β*-unsaturated ketone (**5.16**) was recovered when the latter crude product was subjected to flash column chromatography further supported this assumption.

---

[5.10] For a study on reductive opening of allyl-alcohols epoxides see: Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.

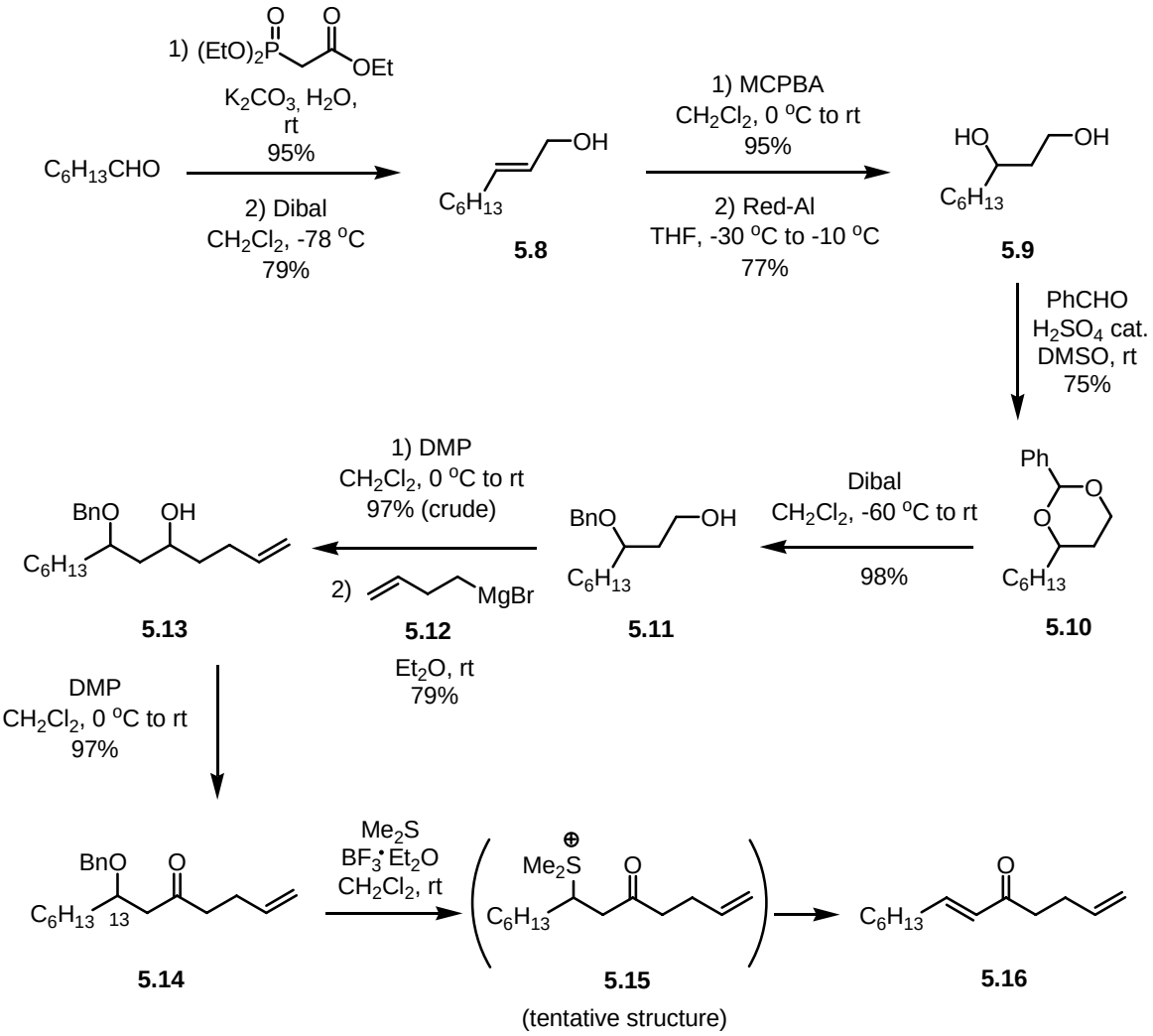
[5.11] For an alternative preparation of benzylidene acetal (**5.10**), see: Nishigaichi, Y.; Takuwa, A. *Tetrahedron Lett.* **2002**, *43*, 3045.

[5.12] (a) For a similar example see: Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593. (b) For a similar transformation, using orthoesters instead of benzylidene acetals, see: Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947.

[5.13] Grignard reagent (**5.12**) was prepared following a literature procedure: (a) For its preparation in $Et_2O$ see: Harding, K.; Burks, S. *J. Org. Chem.* **1984**, *49*, 40. (b) For its preparation in THF see: Nemoto, H.; Shiraki, M.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 1347.

[5.14] Greene, T. W.; Wuts, P. G. M. in "Protective Groups in Organic Synthesis" **1999**, Wiley, New York, 3rd ed..

[5.15] (a) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662. (b) Knops, H.-J.; Born, L. *Tetrahedron Lett.* **1983**, *24*, 2973. (c) Akiyama, T.; Hirofuji, H.; Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 1321.

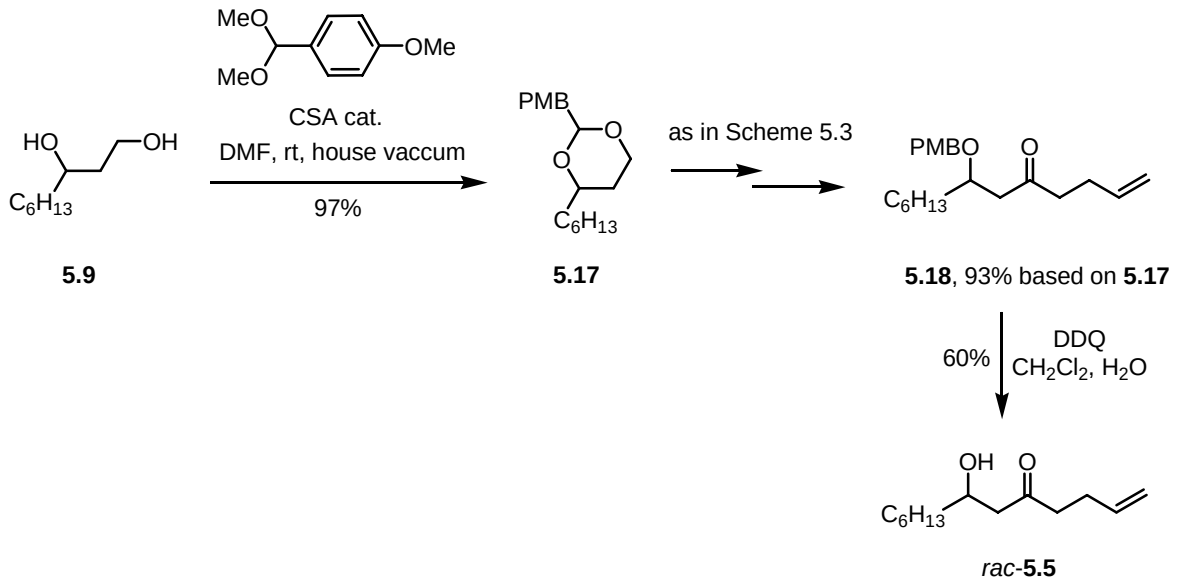



**Scheme 5.3** Preparation of ketone (**5.14**).

Although a setback with respect to the formation of the desired alcohol *rac*-(**5.5**), the (presumed) formation of sulfonium salt (**5.15**) was, at the time, taken as an encouraging signal towards our goal in that it showed that the 13-position of ketone (**5.14**) in is indeed susceptible of nucleophilic displacement.

A simple solution to this problem, which allowed keeping the same overall synthetic strategy, was found by switching to the PMB protecting group (Scheme 5.4). The required PMB-acetal (**5.17**), obtained in high yield (97%) from diol (**5.9**) and the dimethylacetal of *p*-anisaldehyde in the presence of a catalytic amount of CSA by continuously distilling off MeOH, was converted into PMB-ketone (**5.18**) by a similar sequence of steps as used for the preparation of Bn-ketone (**5.14**). Removal of the

PMB group from (**5.18**) was accomplished in 60% yield by the use of DDQ, hence producing alcohol *rac*-(**5.7**).[5.16,5.17,5.18]

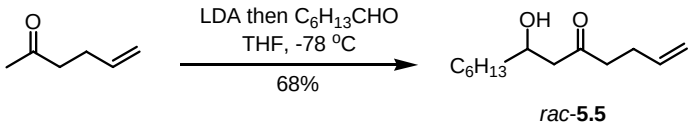



**Scheme 5.4** Preparation of *rac*-(**5.5**).

Importantly, Kitching and co-workers already demonstrated that both enantiomers of the epoxide obtained from allylic alcohol (**5.8**) can be obtained in pure form by means of the SAE reaction.[5.9] Therefore, the present synthetic route can easily be adapted to prepare the required alcohol (*R*)-(**5.5**).

[5.16] Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

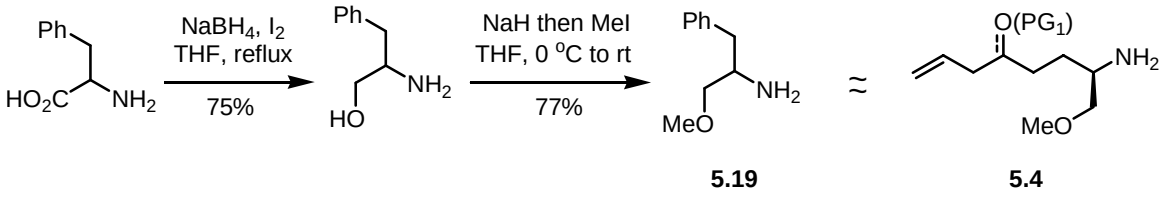
[5.17] Alcohol *rac*-(**5.5**) was routinely prepared by the aldol reaction of the kinetic lithium enolate of allylacetone, obtained by treating the latter with LDA at -78 °C,[5.18] with heptaldehyde (**Scheme 5.B**).




**Scheme 5.B** Preparation of alcohol *rac*-(**5.5**).

[5.18] For the preparation of the kinetic enolate of allyl acetone, see: Hoffmann, R. W.; Kahrs, B. C.; Schiffer, J.; Fleschhauer, J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2407.

Regarding amine (**5.4**), it was decided to initially use simpler surrogates for this building block. Model amines to be employed were derived from amine (**5.19**). The latter was prepared from phenylalanine by initial reduction to phenylalalinol using the conditions reported by Meyers and McKennon ($NaBH_4$-$I_2$ in refluxing THF, 75% yield).[5.19] Subsequent methylation of the hydroxyl functionality was accomplished using standard conditions for this transformation (NaH then MeI, 77% yield).[5.20] The amino group was then conveniently functionalized (*vide infra*, section 5.1.1.3).




**Scheme 5.5** Preparation of model amine (**5.19**).

We were now in conditions to test the challenging coupling reaction between alcohol *rac*-(**5.5**) and a suitable form of amine (**5.19**).

### 5.1.1.3 Model Studies Pertaining to the Displacement Reaction Strategy

The displacement reaction was first attempted using Mitsunobu conditions. The Mitsunobu reaction is a useful method in organic synthesis whereby a hydroxy group is (stereospecifically) replaced by a variety of nucleophiles using the redox couple of a tertiary phosphine and a diazocompound.[5.21]

Ragnarsson and co-workers showed that the yields in Mitsunobu reactions correlate well with the pKa of the nucleophilic reagent,[5.22] which typically has to be approximately 11 for the reaction to proceed satisfactorily. Therefore, and using as guides the pKas of *N*-methyltosylamide (11.7)[5.23] and *N*-methyltriflamide (7.5),[5.24]

---

[5.19] McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.

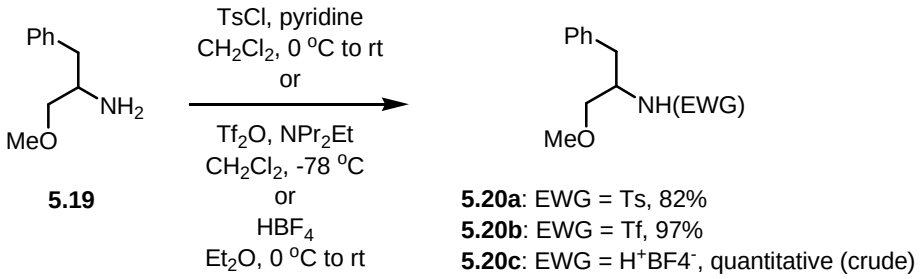
[5.20] Model amine (**5.19**) was prepared from phenylalalinol using a modification of the following literature procedure: Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892.

[5.21] For selected reviews on the Mistunobu reaction, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. Reactions* **1992**, *42*, 335. (c) Castro, B. R. *Org. Reactions* **1983**, *29*, 1.

[5.22] (a) Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L.; Ragnarsson, U. *J. Org. Chem.* **1991**, *56*, 7172. (b) Koppel, I.; Koppel, J.; Leito, , I.; Phil, V.; Wallin, A.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans 2* **1993**, 655.

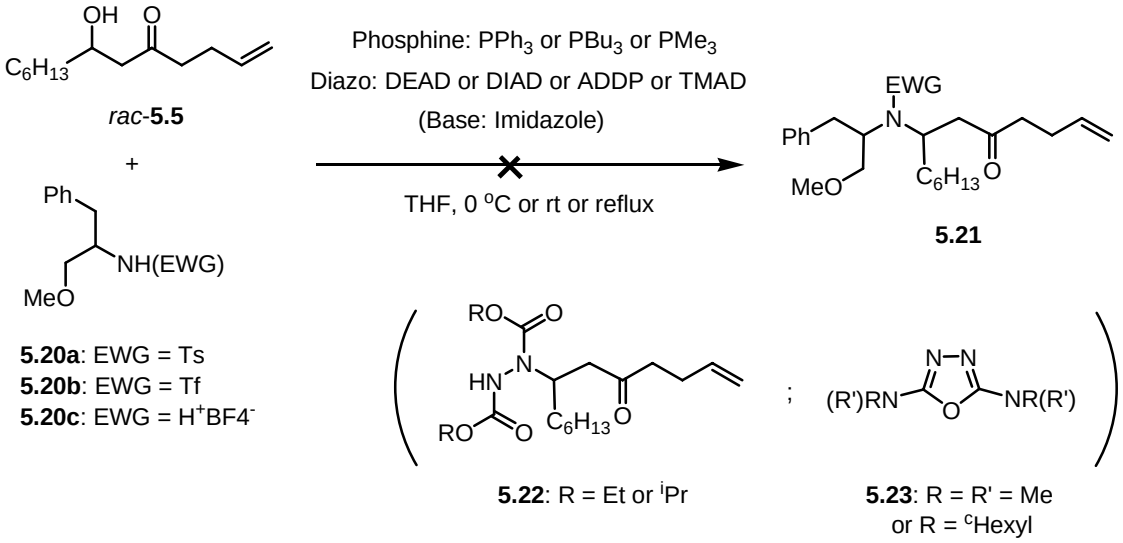
[5.23] Dauphin, G.; Kergomard, A. *Bull. Soc. Chim. Fr.* **1961**, 486.

tosylamide (**5.20a**) and triflamide (**5.20b**) were thought to be suitable amine-type nucleophiles for the intended Mitsunobu reaction. Toslyamide (**5.20a**) was prepared in 82% yield from model amide (**5.19**) by standard treatment with TsCl in the presence of pyridine; triflamide (**5.20b**) was obtained from the reaction of amine (**5.19**) with $Tf_2O$ in the presence of $N^iPr_2Et$ at low temperature (-78 °C) in 97% yield (Scheme 5.6).




**Scheme 5.6** Preparation of (protected/activated) amines (**5.20**).

The Mitsunobu reaction of alcohol *rac*-(**5.5**) with activated amines (**5.20**) was then investigated under a variety of conditions (Scheme 5.7).



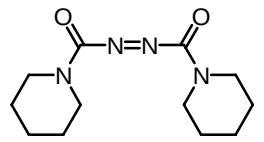

**Scheme 5.7** (Attempted) Mitsunobu reaction between alcohol *rac*-(**5.5**) and amines (**5.20**).

[5.24] Trepka, R. D.; Harrington, J. K.; Belisle, J. W. *J. Org. Chem.* **1974**, *39*, 1094.

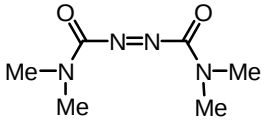
Under standard Mitsunobu conditions (1.5 equivalents equimolar excess of alcohol, $PPh_3$ and DEAD (or DIAD) relative to the protected amine component; various orders of addition) the desired amine (**5.21**) was never produced. $P(O)Ph_3$ and alkylated hydrazine derivatives (**5.22**) were occasionally isolated and/or detected by mass spectrometry.

In an attempt to promote the desired reaction, and to simultaneously avoid the formation of the latter hydrazo by-products, it was argued that the nucleophilicity of the hydrazide anion had to be decreased. This could in theory be accomplished by using a salt of amine (**5.19**) which would provide a proton to quench the hydrazo anion.[5.25] Ideally, a non-nucleophilic counter anion is desirable and so the tetrafluoroborate salt (**5.20c**) emerged as a good candidate. This salt, prepared by treating amine (**5.19**) with $HBF_4$, proved to be very hygroscopic and typically it was dried over phosphorous $P_2O_5$ before use. Unfortunately, the use of the amine salt (**5.20c**) also failed to deliver amine (**5.21**) (Scheme 5.7).

In the early 1990s, various modifications of the classical Mitsunobu conditions were reported: the Tsunoda-Itô group introduced several more reactive azodicarboxamides/phospines redox systems to be used in Mitsunobu couplings, such as ADDP/$PBu_3$ and TMAD/$PBu_3$ (Figure 5.2);[5.26] another variation that emerged with respect to the original Mitsunobu conditions consists in the use of exogenous weak bases[5.27a] (in particular, Falk and co-workers described the application of ADDP/$PMe_3$ in the presence of imidazole as being useful in problematic Mitsunobu reactions).[5.27b]




ADDP




TMAD

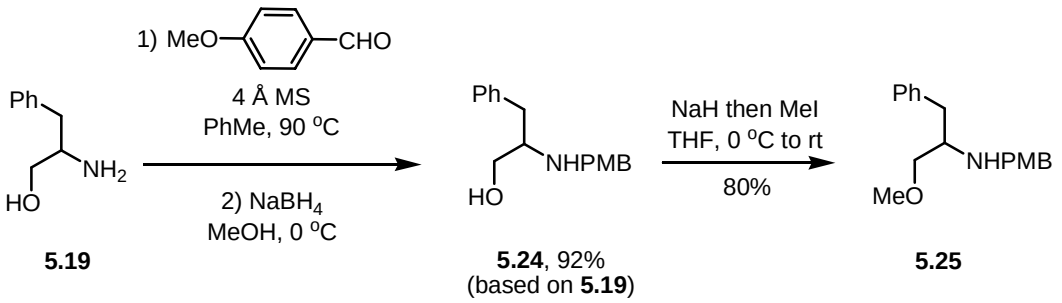
**Figure 5.2** Structures of ADDP and TMAD.

These improved Mitsunobu conditions were also tested, namely the use of ADDP and TMAD combined with $PBu_3$ or $PMe_3$, with and without imidazole. Disappointingly, once again *rac*-(**5.5**) alcohol proved to be refractory with respect to the desired

[5.25] For a precedent for this type of approach see: Sammes, P, G.; Smith, S. *J. Chem. Soc., Perkin Trans 1* **1984**, 2415.
[5.26] (a) Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639. (b) Tsunoda, T.; Otsuka, O.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539.
[5.27] (a) Campbell, D. A.; Bermak, J. C. *J. Org. Chem.* **1994**, *59*, 658. (b) Lai, J.-Y.; Yu, J.; Hawkins, D.; Falck, J. R. *Tetrahedron Letts.* **1995**, *36*, 5691.

displacement reaction and amine (**5.21**) was never isolated. Under these conditions, compounds tentatively identified as oxadiazoles (**5.23**) were occasionally obtained from the crude reaction mixture and/or identified by MS (Scheme 5.7).

As a last effort, the desired displacement reaction was attempted using "conventional" $S_N2$ conditions.[5.28] For this case, and in addition to amine (**5.19**), model amine (**5.25**) was also employed. The latter was readily prepared by the following sequence: reductive amination[5.29] of amine (**5.19**) with *p*-methoxybenzaldehyde and $NaBH_4$ delivered the known amine (**5.24**)[5.30] followed by methylation of the hydroxy functionality using standard conditions (NaH then MeI) (Scheme 5.8).




**Scheme 5.8** Preparation of model amine (**5.25**).

The use of standard $S_N2$ conditions requires the conversion of the hydroxyl group into a labile nucleofuge, such as the corresponding mesylates and triflates. Accordingly, treatment of alcohol *rac*-(**5.5**) with MsCl in pyridine at -5 °C to 0 °C afforded mesylate (**5.26a**), which was used as the crude product. Triflate (**5.26b**), obtained by treatment of *rac*-(**5.5**) with $Tf_2O$ in the presence of 2,6-lutidine at -78 °C,[5.31] was also used directly in subsequent reactions (Scheme 5.9).

---

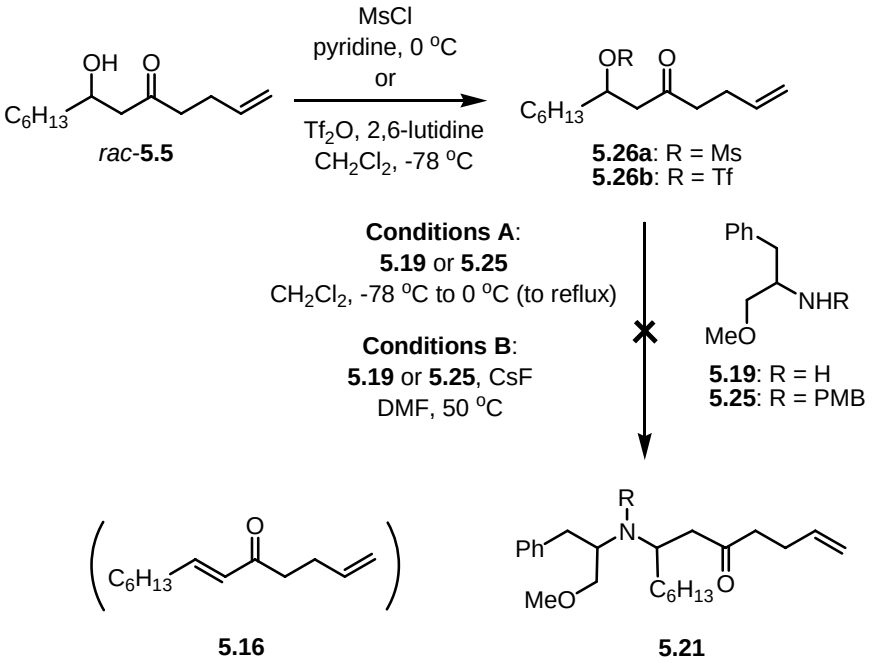
[5.28] For selected examples where amines are prepared by a $S_N2$ reaction from triflates or mesylates see: (a) Bloch, R.; Brillet-Fernandez, C.; Mandville, G. *Tetrahedron: Asymmetry* **1994**, *5*, 745. (b) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755. (c) Feenstra, R. W.; Stokkingreef, E. H. M.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron* **1988**, *44*, 5583. (d) Walker, M. A. *Tetrahedron* **1997**, *53*, 14591. (e) Effenberger, V. F.; Burkard, U.; Willfahrt, J. *Angew. Chem.* **1983**, *95*, 50. (f) Kowollik, W.; Janairo, G.; Voelter, W. *J. Org. Chem.* **1988**, *53*, 3943.

[5.29] For an excellent review on reductive amination, see:Baxter, E. W.; Reitz, A. B. *Organic Reactions* **2002**, *59*, 1.

[5.30] Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074.

[5.31] (a) Feenstra, R. W.; Stokkingreef, E. H. M.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron Lett.* **1987**, *28*, 1215. (b) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283. These papers acknowledge the importance of using either 2,6-lutidine or 2,6-di-$^t$butyl-4-methyl-pyridine as bases in the preparation

The coupling reaction between mesylate (**5.26a**) or triflate (**5.26b**) and amines (**5.19**) or (**5.25**) was then tested. Two set of conditions were used: either the two reactants were simply stirred together in $CH_2Cl_2$ at various temperatures (conditions A) or the displacement reaction was performed using the conditions reported by Otera and co-workers,[5.32] *i.e.*, the reaction was carried in the presence of an excess CsF in DMF at 50 $^oC$ (conditions B). Not totally unexpectedly, the desired secondary amine (**5.21**) was never produced and typically the elimination product, (*E*)-*α,β*-unsaturated ketone (**5.16**), was obtained (Scheme 5.9).




**Scheme 5.9** (Attempted) $S_N2$ reaction between alcohol *rac*-(**5.5**) and amines (**5.19**) and (**5.25**).

In view of these disappoint results, the displacement approach was abandoned.

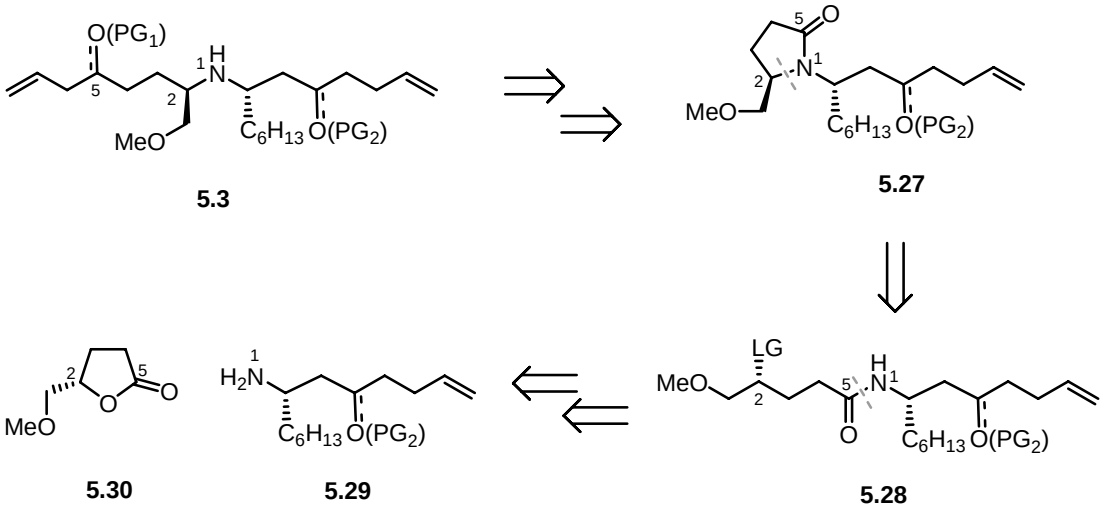
of labile triflates. (c) For a general reference regarding triflates see: Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

[5.32] Otera, J. ; Nakazawa, K.; Sekoguchi, K.; Orita, A. *Tetrahedron* **1997**, *53*, 13633.

## 5.1.2 Synthetic Studies Towards Diene (5.3) *via* the Opening of a Lactam

### 5.1.2.1 Retrosynthetic Considerations

In another approach investigated, diene (**5.3**) was envisioned to derive, after functional group manipulation, from the opening of chiral lactam (**5.27**). The latter was to be prepared from amide (**5.28**) by means of an intramolecular displacement reaction. Amide (**5.28**) would be derived from the reaction between chiral amine (**5.29**) and chiral lactone (**5.30**) (Scheme 5.10). Thus, in the present synthetic plan the sense of the coupling partners is the opposite with respect to the "displacement reaction approach" previous investigated (*vide supra*, Section 5.1.1).

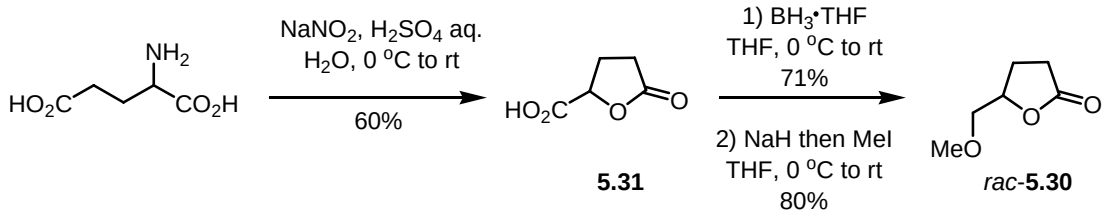



**Scheme 5.10** Simplified retrosynthetic analysis for diene (**5.3**) based on the opening of a lactam.

### 5.1.2.2 Preparation of the Building Blocks Pertaining to the Lactam Opening Approach

For convenience, initial studies were again performed using racemic materials.

The synthesis of lactone *rac*-(**5.30**) was accomplished as depicted in Scheme 5.11. Following a literature procedure by Larcheveque and Lalande,[5.33] glutamic acid was first treated with $NaNO_2$ in an aqueous solution of $H_2SO_4$ to afford lactone (**5.31**) in 60% yield. Reduction of the carboxylic acid functionality with $BH_3$·THF delivered the corresponding hydroxymethyl-γ-butyrolactone (not shown) in 71% yield.[5.33,5.34] Methylation using standard conditions (NaH followed by treatment with MeI) finally produced lactone *rac*-(**5.30**) in 80% yield.

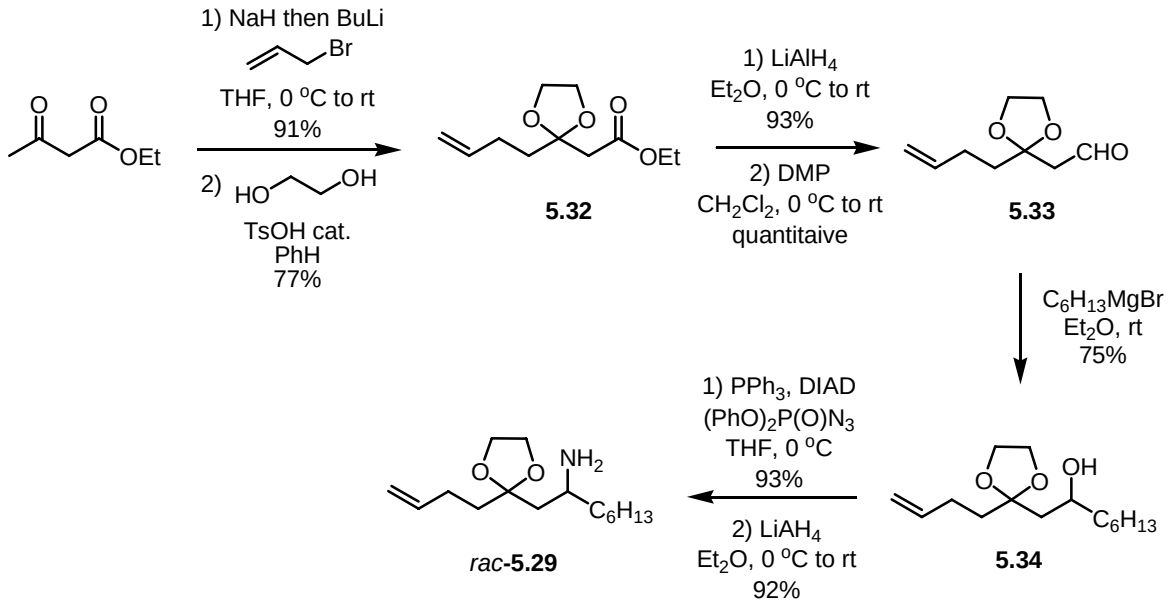



**Scheme 5.11** Preparation of lactone *rac*-(**5.30**).

The second building block required to implement the current strategy, amine *rac*-(**5.29**), was prepared according to the sequence shown in Scheme 5.12. Following a procedure by Weiler and Huckin,[5.35] treatment of ethylacetoacetate with NaH (1 eq.) followed by BuLi (1 eq.) generated the corresponding dianion which, upon reaction with allyl bromide, afforded the γ-allylated product in good yield (91%). Protection of the keto functionality as the corresponding dioxalane (**5.32**) was accomplished using the conditions reported by Baldwin and co-workers (ethyleneglycol in the presence of a catalytic amount of TsOH in refluxing benzene)[5.36] and proceeded in good yield (77%). Reduction of the ester group with $LiAlH_4$, followed by Dess-Martin oxidization of the resulting crude alcohol underwent uneventfully delivering the known aldehyde (**5.33**) in excellent overall yield. This compound proved somewhat unstable and was best kept frozen in a benzene matrix. Aldeyhde (**5.33**) was

[5.33] (a) Larcheveque, M.; Lalande, J. *Tetrahedron* **1984**, *40*, 1061. (b) For a slightly different procedure, see: Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449.
[5.34] (*S*)- and (*R*)-Hydroxymethyl-γ-butyrolactone are commercially available from Fluka.
[5.35] Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
[5.36] Baldwin, S. W.; Wilson, J. D.; Aubé, J. *J. Org. Chem.* **1985**, *50*, 4432.

converted into secondary alcohol (**5.36**) in 75% yield by means of a Grignard reaction with hexylMgBr. Conversion of the latter into the corresponding azide (not shown) was accomplished with diphenylphosphoryl azide (DPPA) using standard Mitsunobu conditions ($PPh_3$/DIAD) in high yield (93%).[5.37] The high nucleophilicity of the azide anion, together with its "needle" shape no doubt were key factors for the success of this transformation and this stands in sharp contrast with the results obtained in Section 5.1.1.3. It is interesting to note that the source of the azide anion is of key importance for the high yield obtained in this displacement reaction: when $ZnN_6 \cdot 2Py$, prepared from $Zn(NO_3)_2$, $NaN_3$ and pyridine according to the procedure of Rollin and Viaud,[5.38] was used not only was the reaction more sluggish, but it could never be driven to completion. The desired *rac*-(**5.29**) amine was finally obtained in high yield (92%) by reduction of the corresponding azide with $LiAlH_4$.

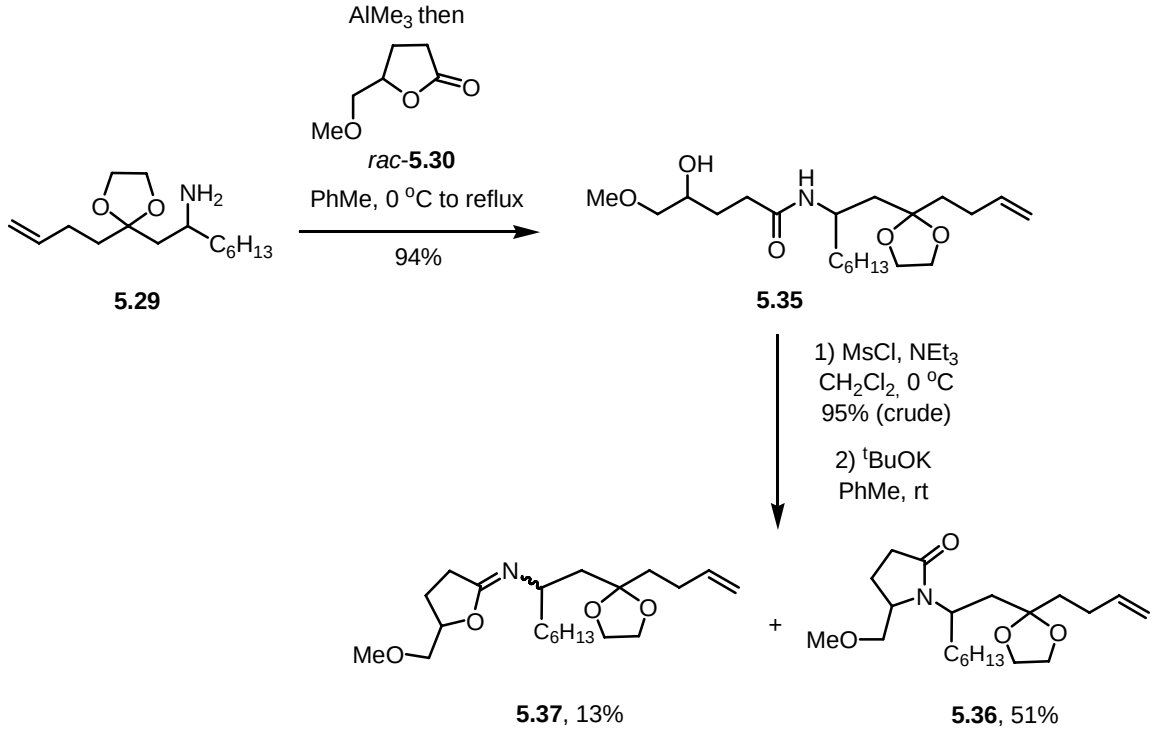



**Scheme 5.12** Preparation of amine *rac*-(**5.29**).

[5.37] Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977.
[5.38] Rollin, P.; Viaud, M. C. *Synthesis* **1990**, 130.

### 5.1.2.3 Implementation of the Lactam Opening Approach

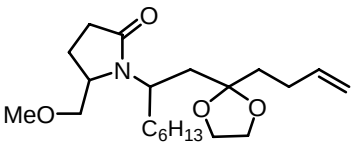
We were now ready to test the coupling of amine *rac*-(**5.29**) and lactone *rac*-(**5.30**). After some unsuccessful attempts, it was found that the desired amide (**5.35**) could be obtained in excellent yield (94%) when the reaction between *rac*-(**5.29**) and *rac*-(**5.30**) was performed using the conditions reported by Weinreb and co-workers ($AlMe_3$ in refluxing toluene)[5.39] (Scheme 5.13). Presumably, under these conditions a nucleophilic aluminum-amide species is formed which, due to the Lewis acidic nature of aluminum, activated the lactone towards ring opening. Treatment of lactam (**5.35**) with MsCl in the presence of $NEt_3$ afforded the corresponding mesylate (not shown) which was directly subjected to a $^t$BuOK-promoted intramolecular aminocyclization affording the desired lactam (**5.36**) in 51% yield. Due to the ambidentate nature of the amide anion generated, imine (**5.37**), the product of *O*-alkylation was also isolated in 13% yield. The two alkylation products, lactam (**5.36**) and imine (**5.37**), were readily separated by flash chromatography.



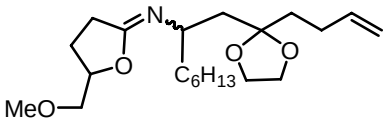

**Scheme 5.13** Preparation of lactam (**5.36**).

[5.39] (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

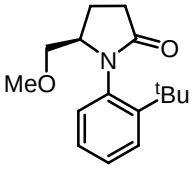
The distinction between the products of *N*- and *O*-alkylation, lactam (**5.36**) and imine (**5.37**), respectively, was made by comparison with reported spectral data for similar compounds. In particular, the $^{13}C$ signal for the lactam carbon and the characteristic infrared (IR) frequency of the lactam carbonyl were considered. Hence, the values obtained for (**5.36**) at 176.2 ppm and 1684 $cm^{-1}$, respectively, are in good agreement to the values reported by Taguchi and co-workers for pyrrolidinone (**5.38**) (176.5 ppm and 1685 $cm^{-1}$),[5.40a] to that of pyrrolidinones (**5.39**) (174.4 ppm)[5.40d] and (**5.41**) (1688 $cm^{-1}$)[5.40b]. On the other hand, the values produced by iminotetrahydrofuran (**5.37**) at 170.3 ppm and 1725 $cm^{-1}$ are closer to the tabulated values for iminoethers (**5.40**) (169.2 ppm) and reported by Saegusa and co-workers for (**5.42**) (1712 $cm^{-1}$).[5.40c]



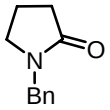

**5.36**
$^{13}C$ 176.2 ppm
IR (neat) 1684 $cm^{-1}$



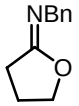

**5.37**
$^{13}C$ 170.3 ppm
IR (neat) 1725 $cm^{-1}$



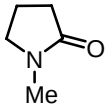

**5.38**
$^{13}C$ 176.5 ppm
IR (neat) 1685 $cm^{-1}$



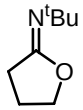

**5.39**
$^{13}C$ 174.4 ppm




**5.40**
$^{13}C$ 169.2 ppm




**5.41**
IR (neat) 1688 $cm^{-1}$

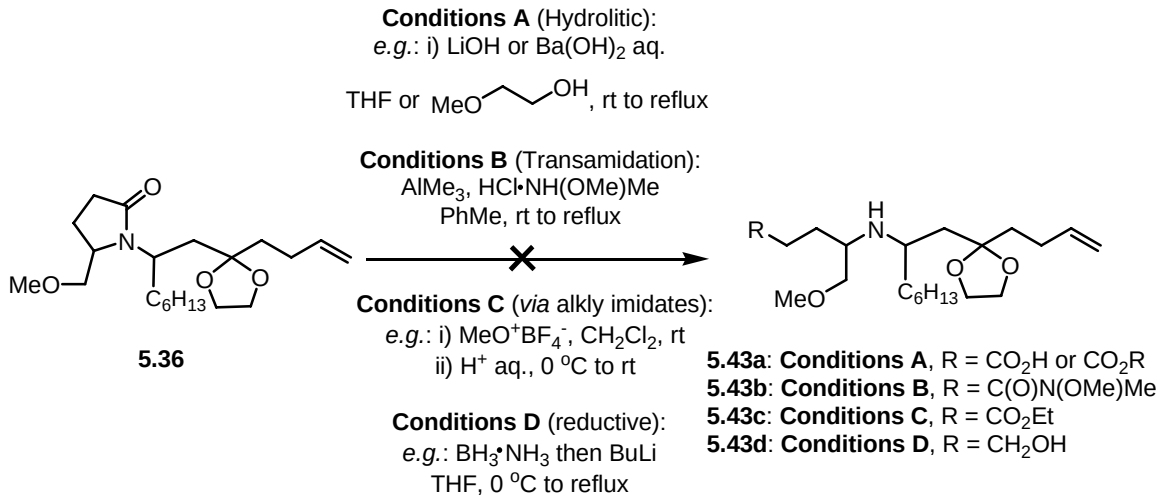



**5.42**
IR (neat) 1712 $cm^{-1}$

**Figure 5.3** (Selected) $^{13}C$ and IR values for pyrrolidinones and iminotetrahydrofurans.

The next step in the planned synthetic route consisted in the opening of lactam (**5.36**). Several conditions were investigated for this transformation and the most important are shown in Scheme 5.14.

[5.40] (a) Fujita, M.; Kitagawa, O.; Yamada, Y.; Izawa, H.; Hasegawa, H.; Taguchi, T. *J. Org. Chem.* **2000**, *65*, 1108. (b) Dolphin, D.; Wick, A. in "Tabulation of Infrared Spectral Data" **1977**, John Wiley, New York. (c) Saegusa, T.; Taka-Ishi, N.; Ito, Y. *Synthesis* **1970**, 475. (d) Deyrup, J. A.; Gingrich, H. L. *J. Org. Chem.* **1977**, *42*, 1015.




**Scheme 5.14** (Attempted) opening of lactam (**5.36**).

We began with hydrolytic methods, which were expected to afford the carboxylic acid (**5.43a**) (or an equivalent form) (conditions A). Basic hydrolysis with KOH or $Ba(OH)_2$ in THF or 2-methoxyethanol (at room temperature or at reflux) yielded only starting material.[5.41a,b] The same disappointing result was obtained by the use of Gassaman's "anhydrous KOH" method in refluxing THF.[5.41c] The LiOOH protocol of Evans, which capitalizes in the enhanced nucleophilicity of the peroxide anion and is reported to be notoriously insensitive to substrate steric effects, also failed to promote the lactam-opening and only lactam (**5.36**) was recovered.[5.41d] Acidic hydrolysis was also tried: [5.41e] aqueous HCl (6 M) at room temperature cleaved the dioxalane protecting group affording the corresponding ketone; under reflux extensive decomposition occurred.

Transamidation of lactam (**5.36**) to the corresponding Weinreb amide (**5.43b**) was next attempted by treating the former with HN(OMe)Me and $AlMe_3$ in refluxing toluene (conditions B).[5.42,5.43] Unfortunately, the starting lactam proved to be inert towards these conditions.

---

[5.41] For selected examples see: (a) Ames, D. E.; Islip, P. J. *J. Chem. Soc.* **1961**, 351. (b) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1657. (c) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275. (d) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141. (e) Knight, D. W.; Lewis, N.; Share, A. C.; Haigh, D. *J. Chem. Soc., Perkin Trans 1* **1998**, 3673.

[5.42] For the analogous conversion of esters/lactones to the corresponding Weinreb amide, see: (a) Ref. 5.39. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commu.* **1982**, *12*, 989. (c) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685. (d) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

Amides/lactams can undergo *O*-alkylation with Meerwein's reagents (*e.g.*, trimethyloxonium tetrafluoroborate) to afford the corresponding iminoether fluoroborates which can be hydrolyzed in aqueous acid or base (conditions C).[5.44a,b] In 1998, Charette and Chua reported a conceptually similar approach involving the use of $Tf_2O$ and (excess) EtOH to convert tertiary amides into the corresponding alkyl imidates, which upon aqueous work up undergo hydrolysis to carboxylic esters.[5.44c] Disappointingly, for the case of lactam (**5.36**), both set of conditions only produced an intractable mixture.

The final attempt to open lactam (**5.36**) was performed with $LiH_2NBH_3$,[5.45a] prepared *in situ* from the $BH_3{\cdot}NH_3$, BuLi and $LiBHEt_3$ (conditions D).[5.45b] This reagent is reported to convert tertiary amides into the corresponding primary alcohol in good yields. However, the only identifiable product obtained when lactam (**5.36**) was subjected to these reductive conditions was the corresponding pyrrolidine.

On the basis of these disappointingly results, the lactam-opening approach was discontinued.

---

[5.43] For general reviews concerning the use of Weinreb's amide, see: (a) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340. (b) Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15. (c) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339*, 517.

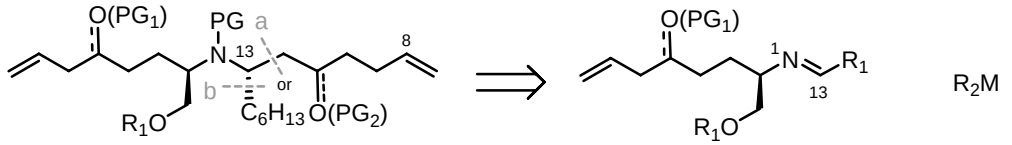
[5.44] (a) Meerwein, H.; Hinz, G.; Fuchs, O.; Sassa, H. J.; Schrodt, H.; Spille, J. *Chem. Ber.* **1956**, *89*, 2060. (b) Meerwein, H.; Behling, J.; Grethe, G.; Rogalski, W. *J. Am. Chem. Soc.* **1967**, *89*, 4991. (c) Charette, A. B.; Chua, P. *Synlett* **1998**, 163.

[5.45] (a) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623. (b) Brown, H. C.; Kim, S. C. *Synthesis* **1977**, 635.

## 5.1.3 Synthetic Studies Towards Diene (5.3) *via* the Addition of Organometallic Reagents to a Chiral Aldimine

### 5.1.3.1 Retrosynthetic Considerations

An alternative strategy investigated to prepare diene (**5.3**) had as the key step the addition of an organometallic reagent (**5.45**) to the azomethine carbon of chiral aldimine (**5.44**) (Scheme 5.15).[5.46]




**5.3** **5.44** **5.45**

**Scheme 5.15** Simplified retrosynthetic analysis for diene (**5.3**) based on a stereoselective organometallic addition to chiral aldimine (**5.44**).

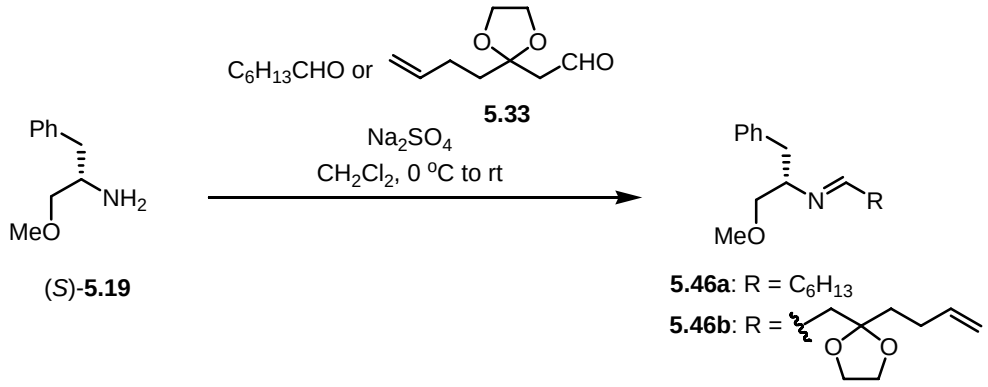
The use of chiral aldimine (**5.44**), which has a (potential) metal-chelating *β*-hydroxy functionality, would in principle allow the diastereofacial selectivity of the addition to be determined by the judicious choice of the organometallic reagent used. Hence, both C13-epimers could in theory be selectively prepared depending on the addition reaction proceeding under chelation control or nonchelation control.

In spite of the attractiveness of this strategy, organometallic additions to the C=N bonds of imines can be severely limited both by the poor electrophilicty of the azomethine carbon and by the tendency of *α*-enolizable imines such as (**5.44**) to undergo deprotonation rather then addition.[5.46] Therefore, model studies were initially conducted to establish the feasibility of such an approach.

[5.46] For selected reviews concerning the addition of organometallic reagents to C=N bonds see: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (b) Volkmann, R. A. in "Comprehensive Organic Synthesis" (Trost. B. M.; Fleming, I., ed.) **1991**, *1*, 355, Pergamon, New York. (c) Volkmann, R. A. In "Comprehensive Organic Synthesis" (Trost. B. M.; Fleming I., ed.) **1991**, *2*, 975, Pergamon, New York. (d) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (d) Denmark, S. E.; Nicaise, O. J. C. *J. Chem. Soc., Chem. Commun.* **1996**, 999. (e) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

### 5.1.3.2 Model Studies Pertaining to the Aldimine Approach

Model studies were conducted with aldimines (*S*)-(**5.46a**) and (*S*)-(**5.46b**). These compounds were readily prepared by condensation of enantiomerically pure amine (*S*)-(**5.19**) with heptaldehyde and aldehyde (**5.33**), respectively, in the presence of anhydrous $Na_2SO_4$ (Scheme 5.16). It should be appreciated that each of these imines represents different senses of disconnection with respect to accessing diene (**5.3**). Thus, whereas the use of hexyladimine (**5.46a**) corresponds to *disconnection a* in Scheme 5.15, aldimine (**5.46b**) embodies the alternative *disconnection b*.




**Scheme 5.16** Preparation of model aldimines (**5.46a**) and (**5.46b**).

The crude imines obtained were used for the subsequent reaction without further purification. The imine linkages were assumed to have the (*E*)-configuration based upon their $^1$H-NMR spectra which showed only a single resonance for the imine proton. A mixture of *E* and *Z* imines would be expected to exhibit different chemical shifts.

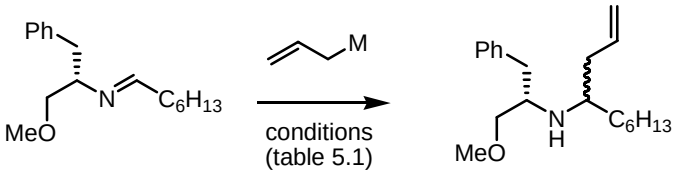
With imines (*S*)-(**5.46a**) and (*S*)-(**5.46b**) in hand, the (diastereoselective) addition of several organometallic reagents was investigated.

A class of organometallic reagents that performs particularly well in 1,2-addition to the azamethine linkage is allylic organometallics.[5.47] The expected homoallylic

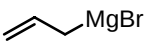
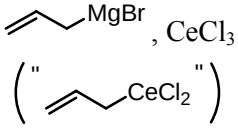
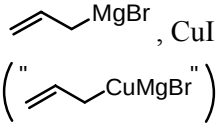
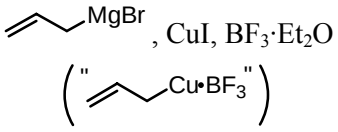
[5.47] For a review on allylic reagents see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. For selected examples related with the use of allylic organometallics with imines see: (b) Alvaro, G.; Boga, C. Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc. Perkin Trans. 1* **1996**, 875. (c) Tanaka, M.; Inoue, K.; Pokorski, U.; Taniguchi, M.; Torii, S. *Tetrahedron Lett.* **1990**, *31*, 3023. (d) Bocoum, A.; Savoia, D.; Ulmani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1542. (e) Ukaji, Y.; Kume, K.;

amines can then be further elaborated owing to the various possible transformations of the C=C double bond of the allyl moiety. Therefore, this type of reagents was the first to be investigated using hexylaldimine (*S*)-(**5.46a**) as substrate (Table 5.1).

**Table 5.1** Addition of (selected) allylic organometallics reagents to aldimine (*S*)-(**5.46a**).




(*S*)-**5.46a** **5.47**

| Entry | Conditions | Conditions | Yield (%) | dr[a] |
|---|---|---|---|---|
| 1 |  (4 eq.) | THF -78 °C to rt | 44 | 5:1 |
| 2 |  (2 eq.) | THF -50 °C to rt | 52 | 9:1 |
| 3 |  (5 eq.) | THF -78 °C to rt | 0 | - |
| 4 |  (5 eq.) | THF -78 °C to rt | 56 | 2:1 |

[a] Based on $^1$H-NMR.

Watai, T.; Fujisawa, T. *Chem. Lett.* **1991**, 173. (f) Basilie, T.; Bocoum, A.; Savoia, D.; Ulmani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766. (g) Bocoum, A.; Boga, C.; Savoia, D.; Umani-Ronchi, A. *Tetrahedron Lett.* **1991**, *32*, 1367. (h) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7780.

The reaction of model imine (*S*)-(**5.46a**) with allylMgBr afforded amine (**5.47**) in moderate yield (44%) and with good diastereomeric ratio (dr 5:1), as determined by $^1$H-NMR (entry 1, Table 5.1). Hoping to increase the yield and the selectivity of the addition reaction, less basic allylic reagents were used next. "AllylCeCl$_2$", prepared *in situ* from anhydrous CeCl$_3$ and allylMgBr, reacted with imine (*S*)-(**5.46a**) delivering amine (**5.47**) in somewhat better yield (52%) and with an improved diastereomeric ratio (dr 9:1) (entry 2, Table 5.1).[5.48] "AllylCu·BF$_3$", which presumably activates imines by *N*-coordination, was generated *in situ* from allylMgBr, CuI and BF$_3$.Et$_2$O;[5.49] its reaction with imine (*S*)-(**5.46a**) proceeded smoothly affording the expected secondary amine in moderate yield (56%) and in poor diastereomeric ratio (dr 2:1) (entry 4, Table 5.1). As expected, activation of the C=N imine bond by complexation with BF$_3$ is critical for the reaction to proceed, as demonstrated by the fact that "allylCuMg", prepared *in situ* from allylMgBr and CuI, failed to give the addition product (**5.47**) (entry 3, Table 5.1).

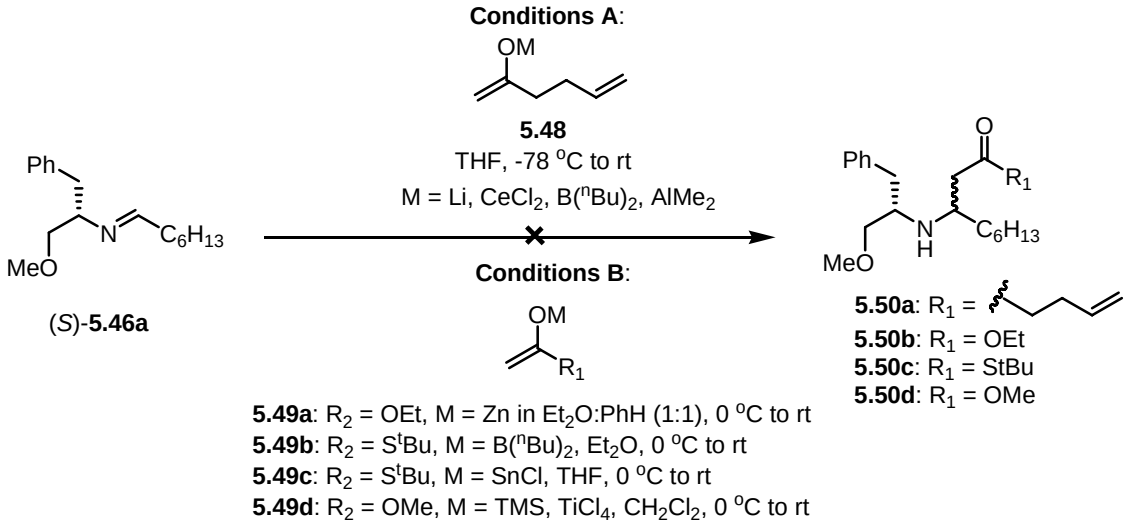
A more convergent approach involving hexylaldimine (*S*)-(**5.46a**) that would avoid the need to manipulate the allylic double bond involves the reaction of the former imine with the kinetic enolate of allylacetone (**5.48**) (conditions A, Scheme 5.17). The reaction of imine (*S*)-(**5.46a**) with the kinetic lithium enolate of allylacetone, obtained by treating the latter with LDA at -78$^o$C,[5.18] failed to deliver the desired secondary amine (**5.50a**) and instead only the starting imine was recovered. Similar disappointing results were obtained with the less basic cerium,[5.50] boron and

[5.48] For selected examples of the use of organocerium reagents with imines see: (a) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 4175. (b) Kobayashi, Y.; Matsumoto, T.; Takemoto, Y. Nakatani, K.; Ito, Y.; Kaimijo, T.; Harada, H.; Terashima, S. *Chem. Pharm. Bull.* **1991**, *39*, 2550. (c) Reetz, M. T.; Jarger, R.; Drewlies, R.; Hübel, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 103. (d) Ukaji, Y.; Watai, T.; Sumi, T.; Fujisawa, T. *Chem. Lett.* **1991**, 1555. (e) Higashiyama, K.; Fujikura, H.; Takahashi, H. *Chem. Pharm. Bull.* **1995**, *43*, 722.

[5.49] For selected examples regarding the reaction of imines with organocopper reagents complexed with BF$_3$ see: (a) Wada, M.; Sakurai, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 1079. (b) Cainelli, G.; Giacomini, D.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1992**, *33*, 7783. (c) Yamamoto, Y. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 947. (d) Ishimaru, K.; Tsuru, K.; Yabuta, K.; Wada, M.; Yamamoto, Y.; Akiba, K. *Tetrahedron: Asymmetry* **1994**, *5*, 2261.

[5.50] For the use of cerium enolates in aldol reactions see: (a) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *Tetrahedron Lett.* **1983**, *24*, 5233. (b) Fukuzawa, S.; Tsuruta, T.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans 1* **1987**, 1473. (c) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. (d) Imamoto, T.; sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, 25, 4233.

aluminium enolates, prepared from the previous lithium species by transmetallation with anhydrous $CeCl_3$, $B(^nBu)_2OTf$ and $AlMe_2Cl$, respectively, in THF at -78 °C.




**Scheme 5.17** (Attempted) reaction of aldimine (*S*)-(**5.46a**) with various enolates.

The condensation of imine (*S*)-(**5.46a**) with several ester enolates was also explored (conditions B, Scheme 5.17).[5.51,5.52] The reaction of the (preformed) Reformatsky reagent (**5.49a**)[5.53] with aldimine (*S*)-(**5.46a**) failed to produce the expected ester (**5.50b**) and only led to the recovery of the starting aldimine. The boron (**5.49b**)[5.54]

[5.51] For selected reviews on the reaction of ester enolates with imines, see: (a) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (c) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.

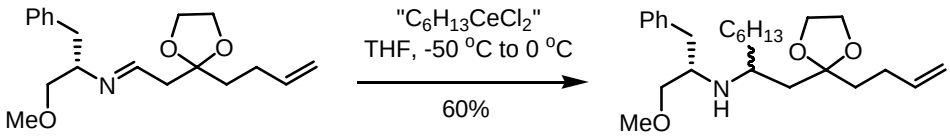
[5.52] For selected examples involving the reaction of *chiral* imines with various ester enolates see: (a) Overman, L. E.; Osawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 1698. (b) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 260. (c) Yamada, T.; Suzuki, H.; Mukaiyama, T. *Chem. Lett.* **1987**, 293. (d) Ojima, I.; Inaba, S. *Tetrahedron Lett.* **1980**, *21*, 2077. (e) Ojima, I.; Inaba, S. *Tetrahedron Lett.* **1980**, *21*, 2081. (f) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; gálvez, J. A. *Tetrahedron Lett.* **2003**, *44*, 9189. (g) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785.

[5.53] For selected examples regarding the reaction of Reformatsky reagents with imines see: (a) Blicke, F. F.; Gould, W. A. *J. Org. Chem.* **1958**, *23*, 1102. (b) Dardoize, F.; Moreau, J.-L.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1972**, 3841. (c) Bosch, J.; Domingo, A.; Lopez, F.; Rubiralta, M. *J. Heterocycl. Chem.* **1980**, *17*, 241. (d) Luche, J.-L.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1971**, 2260.

[5.54] For selected examples involving the use of boron ester enolates of thioesters in imine-aldol reactions, see: (a) Otsuka, M.; Narita, M.; Yoshida, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishida, H.; Saito, S.; Takita, T.; Umezawa, H. *Chem. Pharm. Bull.* **1985**, *33*, 520. (b) Otsuka, M.; Yoshida, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H. *Tetrahedron Lett.* **1981**, *22*,

and the tin (**5.49c**)[5.55] ester enolates, generated from the corresponding thioester with $B(^nBu)_2OTf$ and $N^iPrEt_2$ in $CH_2Cl_2$ and by treating the lithium enolate of butylthioacetate with $SnCl_2$ in THF, respectively, afforded the same disappointing result. The ketene acetal (**5.49d**)[5.56] in the presence of $TiCl_4$ also failed to react with imine (*S*)-(**5.46a**).

The complementary entry to diene (**5.3**), based on the use of aldimine (*S*)-(**5.46b**) and a hexylorganometallic reagent, was next investigated (Scheme 5.18). Whereas the reaction with hexylMgBr,[5.57] hexylLi,[5.58] hexylZnBr and "hexylCu·$BF_3$",[5.49] prepared *in situ* from the corresponding Grignard reagent, CuI and $BF_3{\cdot}Et_2O$, only lead to recovery of the starting imine, the "hexylCe$Cl_2$" reagent,[5.48] generated *in situ* from hexylMgBr and anhydrous $CeCl_3$, afforded the desired amine (**5.51**) in good yield (60%) and with high diastereomeric ratio (9:1, based on $^{13}$C-NMR).




(*S*)-**5.46b** **5.51**, dr 9:1 ($^{13}$C NMR)

**Scheme 5.18** Reaction of model imine (*S*)-(**5.46b**) with "hexylCe$Cl_2$".

2109. (c) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, *52*, 3489. (d) Iimori, T.; Ishida, Y.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2153.

[5.55] For a precedents for the use of tin ester enolates of thioesters with aldimines, see: (a) Yamasaki, N.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1986**, 1013. (b) Yamada, T.; Suzuki, H.; Mukaiyama, T. *Chem. Lett.* **1987**, 213. (c) Mukaiyama, T.; Suzuki, H.; Yamada, T. *Chem. Lett.* **1986**, 915.

[5.56] For selected examples regarding the reaction of ketene acetals with imines see: (a) Colvin, E. W.; Mcgarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157. (b) Ikeda, K.; Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1983**, *24*, 4707. (c) Colvin, E. W.; Mcgarry, D. G. *J. Chem. Soc., Chem. Commun.* **1985**, 539. (d) Ojima, I.; Inaba, S.; Nagai, M. *Synthesis* **1981**, 545. (e) Ojima, I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett.* **1977**, 3643.

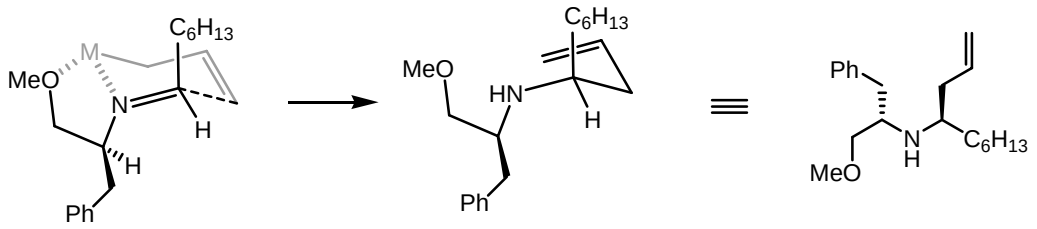
[5.57] For selected examples involving the use of Grignard reagents to imines see: (a) Franz, T.; Hein, M.; Veith, U.; Jäger, V.; Peters, E. M.; Peters, K.; Von Schnering, H. G. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1298. (b) Ref. 5.48d.

[5.58] For selected examples involving the use of lithium reagents to imines see: (a) Hashimoto, Y.; Takaoki, K.; Sudo, A.; Ogasawara, T.; Saigo, K. *Chem. Lett.* **1995**, 235. (b) Ref. 5.48d. (c) Hashimoto, Y. Kobayashi, N.; Kai, A.; Saigo, K. *Synlett* **1995**, 961.

The present results, where only the cerium species succeeded in adding to the azomethine carbon, can be ascribed to the decreased reactivity of alkly organometallics with respect to their allylic counterparts and also to an increase in the acidity of the $\alpha$-protons of the azamethine group in (*S*)-(**4.46b**) due to the inductive effect of the dioxalane oxygens. Therefore, the more basic lithium, magnesium, zinc, and, presumably, the copper reagent are likely to result only in $\alpha$-deprotonation instead of the expected addition.

Although no attempts were made to determine the absolute configuration of the main diastereomer in each of the previous reactions, there are enough precedents in the literature to allow speculation on the sense of the addition for the various organometallic reagents used. Like for carbonyl compounds, the stereoselectivity in the addition of organometallics to imines possessing an adjacent asymmetric center can be predicted/rationalised in terms of a chelation-controlled mechanism or an open-chain model.[5.59]

For the reaction of allyl reagents with imine (*S*)-(**5.46a**) under chelation-controlled conditions, a compact Zimmerman-Traxler cyclic chair transition state (**5.52**) may be proposed. Thus, allyl-magnesium and cerium reagents are likely to simultaneously coordinate the nitrogen and the oxygen atoms of aldimine imine (**5.46a**). The phenyl group is disposed externally and the attack then proceeds to the *Si* face of the imine (Scheme 5.19). Based on these assumptions, the main product of the reaction of imine (*S*)-(**5.46a**) with allylMgBr and "allyl$CeCl_2$" is predicted to have the (*S*,*R*) configuration.

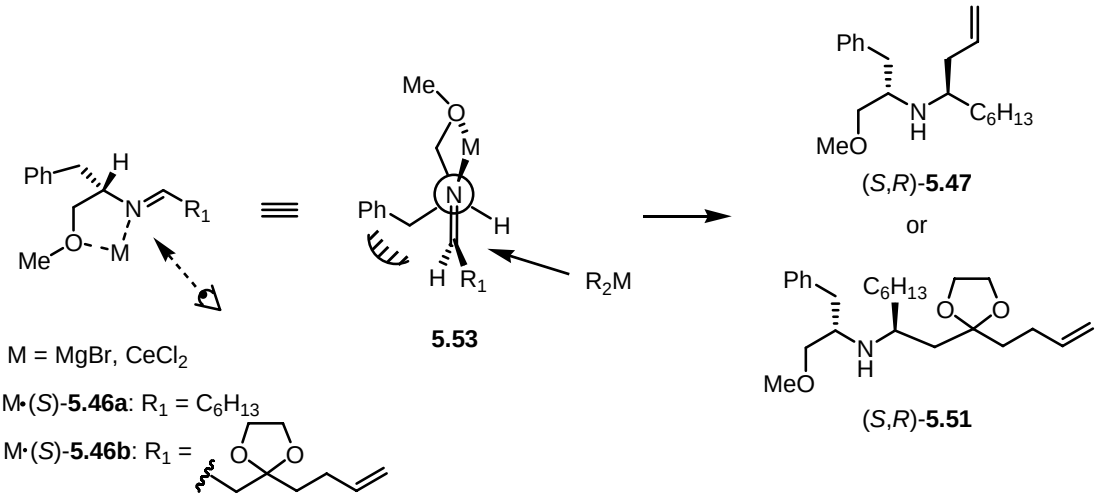



**5.52** (*S*,*R*)-**5.47**

**Scheme 5.19** Cyclic TS (**5.52**) for the addition of allylic organometallics to imine (*S*)-(**5.46a**) under chelation-controlled conditions.

[5.59] See for example, Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

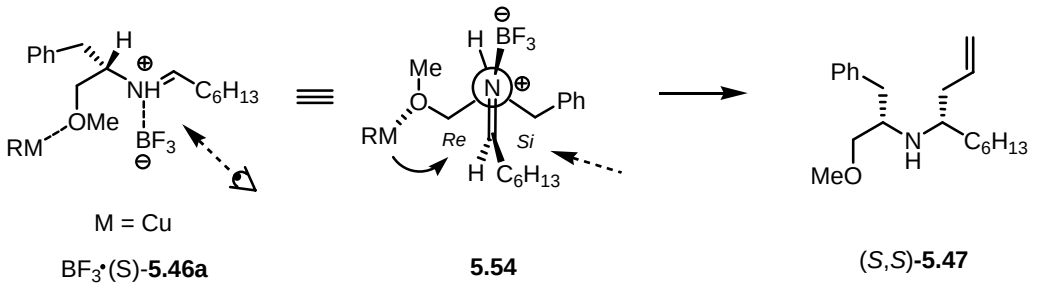
Cram's cyclic model (**5.53**),[5.60] where one equivalent of the Lewis acidic organometallic reagent coordinate simultaneously to the nitrogen and the oxygen atoms of the imine forming an intermediate chelate, is more general and it can be invoked both in the case of (coordinating) allyl and hexyl organometalics; attack of a second equivalent of organometallic reagent then occurs from the less hindered face of this chelate (Scheme 5.20). Based on these assumptions, the main product of the reaction of imine (*S*)-(**4.46a**) with allylMgBr and "allylCeCl$_2$" as well as that of imine (*S*)-(**4.46b**) with "hexylCeCl$_2$" is (also) predicted to have the (*S*,*R*) configuration.




**Scheme 5.20** Chelation-controlled additions of organometallics to aldimines (*S*)-(**5.48**).

On the other hand, in the reaction of aldimine (*S*)-(**5.46a**) with the "allylcopper·$BF_3$" reagent, the simultaneous chelation of the two hetero atoms to the metal is unlikely to occur since the nitrogen lone pair is presumably "tied up" by the LA. In such cases, the "open-chain" model (**5.54**) may be invoked.[5.60] The reaction can then (also) proceed *via* an internal delivery of the (allyl) reagent to the *Re* face of the imine affording the (*S*,*S*)-product (Scheme 5.21).

[5.60] (a) Cram, D. J.; Elhafez, F. A. A. J. Am. Chem. Soc. **1952**, *74*, 5828. (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. For reviews dealing with 1,2-asymmetric induction models for addition to C=X bonds, see: (c) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191. (d) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263. (e) Ager, D. J.; East, M. B. *Tetrahedron* **1992**, *48*, 2803. (f) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556. (g) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678.

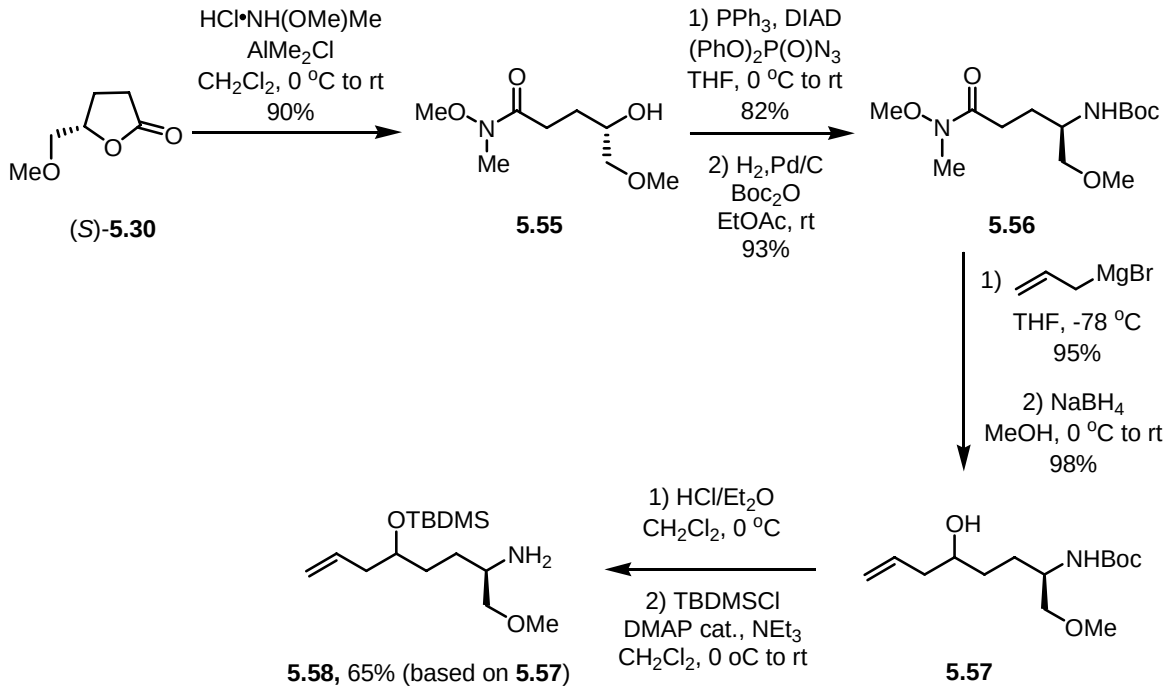



**Scheme 5.21** Non-chellation controlled addition of allylcopper $BF_3$·reagent to (*S*)-(**5.46a**).

## 5.1.3.3 Implementation of the Aldimine Strategy

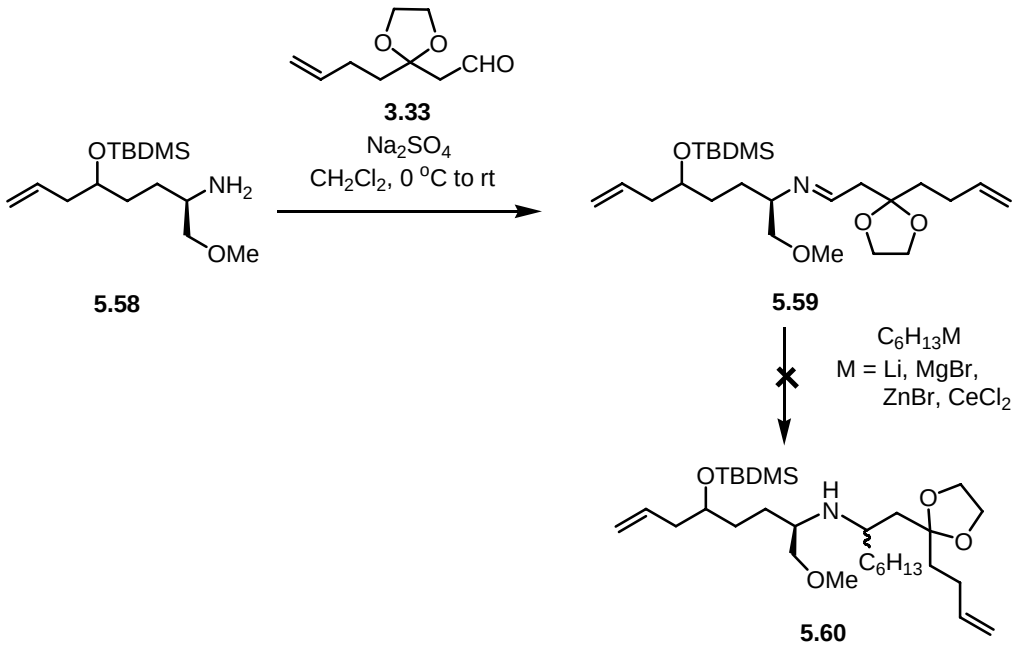
Encouraged by the results obtained in the model studies involving aldimine (**5.46b**) (*vide supra*, Section 5.1.3.2), this strategy was then implemented so as to access diene (**5.3**).

One of the synthetic routes developed to prepare the required amine building block is shown in Scheme 5.22. Chiral lactone (*S*)-(**5.30**), obtained by standard methylation (NaH then MeI, 80% yield) of commercially available (*S*)-hydroxymethyl-γ-butyrolactone, was opened to the Weinreb amide (**5.55**) in high yield (90%) using the conditions reported by Shimizu and co-workers ($AlMe_2Cl$-MeONHMe·HCl in $CH_2Cl_2$ at room temperature).[5.42c,5.43] A Mitsunobu reaction with $PPh_3$, DIAD and DPPA delivered the corresponding azide (not shown) with concomitant inversion of the stereochemistry. A one pot azide-reduction/Boc protection afforded the *N*-Boc amine (**5.56**) in high yield (93%). Reaction of the latter with allylMgBr, immediately followed by $NaBH_4$ reduction of keto functionality (to prevent isomerization of the double bond into conjugation with the carbonyl functionality) afforded alcohol (**5.57**) in excellent combined yield (93%). Exposure of the latter to a solution of HCl in ether, cleaved the carbamate protecting group affording the corresponding hydrochloric salt in 88% yield, which was directly treated with TBDMSCl in the presence of (excess) $NEt_3$ and a catalytic amount of DMAP producing silyl ether (**5.58**) in 65% yield (based on alcohol (**5.57**).




**Scheme 5.22** Preparation of amine (**5.58**).

Condensation of amine (**5.58**) with aldehyde (**5.33**) in the presence of $Na_2SO_4$ afforded aldimine (**5.59**), which was directly subjected to the reaction with various hexylorganometallic reagents (Scheme 5.23). Unfortunately, and in spite of extensive efforts, the addition reaction did not proceed, even when the "hexylCeCl$_2$" reagent that proved successful in the model studies with imine (S)-(**5.46b**) was used.

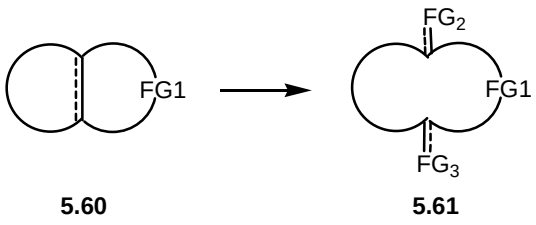



**Scheme 5.23** (Attempted) reaction of aldimines (**5.59**) with various hexylorganometallics.

In view of these results the present approach was suspended.

## 5.2 - Studies Towards Macrocycle (2.12) Based on a Ring Enlargement Reaction

Whereas the previous RCM strategy relied on ring formation, an alternative approach to the synthesis of macrocyles involves ring enlargement processes.[5.61] One of the most used approaches in this context involves the cleavage of a "bridge" (*i.e.*, a single or a double bond) in a bicyclic framework such as (**5.60**) to afford the corresponding ring-expanded system (**5.61**) (Scheme 5.24).

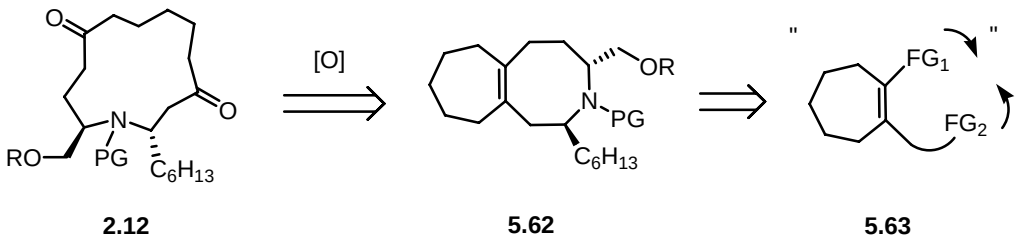



**Scheme 5.24** Ring enlargement *via* the cleavage of "bridge" in a bicyclic system.

[5.61] Hesse, M. in "Ring Enlargement in Organic Synthesis" **1991**, VCH, Weinheim.

## 5.2.1 Retrosynthetic Considerations

Based on this type of ring-enlargement arguments, the key macrocycle diketone (**2.12**) was envisioned to derive from bicycle (**5.62**) by oxidative cleavage of the central double bond.




**2.12** **5.62** **5.63**

**Scheme 5.25** The ring-enlargement approach of bicycle (**5.62**) to key macrocycle (**2.12**).

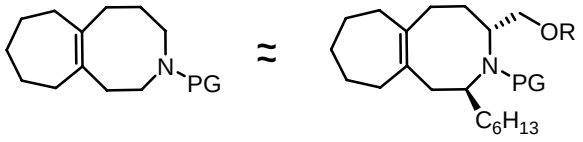
Bicyclic (**5.62**) is unusual in that it contains two "difficult-size" rings, namely a 7- and a 8-membered ring. 8-Membered rings in particular, due to the high degree of ring strain and the transannular interactions present are, arguably, the most difficult to assemble.[5.62,5.63] However, it was argued, on the basis of the Thorpe-Ingold effect, that the a functionalized cycloheptene (**5.63**) would be a convenient precursor to access the bicyclic (**5.62**): the (*cis*)-double bond of the cycloheptene ring (together with the eventual side chains) was/were expected to provide a favorable entropic contribution for the demanding cyclization process.

In view of the uncertainty in accessing the desired bicyclic system *via* the construction of an 8-membered ring, model studies were initially undertaken.

[5.62] Eliel, E. L.; Wilen, S. H. in "Stereochemistry of Organic Compounds" **1994**, Wiley, New York.
[5.63] For leading reference concerning synthetic approaches to 8-membered rings see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.

## 5.2.2 Model Studies Pertaining to the Ring-Enlargement Approach

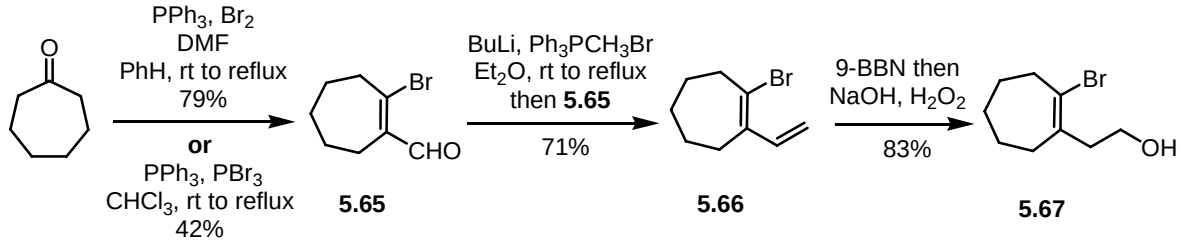
Bicyclic amine (**5.64**) was chosen as a simpler surrogate of (**5.62**) to test the feasibility of such approach (Figure 5.4).




**5.64** **5.62**

**Figure 5.4** Bicyclic (protected) amine (**5.64**) as a model for bicyclic (protected) amine (**5.62**).

We began our studies by preparing a convenient functionalized cycloheptene derivative, bromo alcohol (**5.67**), which would be used as departure point in the present approach. For this purpose, cycloheptanone was reacted with the Vilsmeier salt $Me_2N^+$=CHBr·$Br^-$,[5.64] generated *in situ* by the reaction of $PPh_3$, $Br_2$ and DMF, to afford the known bromoaldeyhde (**5.65**)[5.65] in good yield (79%) and in multigram amounts. Alternatively, the above Vilsmeier salt was prepared *in situ* from $PBr_3$ and DMF. This approach, although delivering the bromoaldehyde (**5.65**) in significantly lower yield (approximately 49%), has the advantage that, apart from an aqueous work up, no purification is required. The bifunctional bromoaldehyde (**5.65**) was then converted to diene (**5.66**) in 71% yield *via* a Wittig methelenation reaction with the ylide obtained from treating methyltriphenylphosphoniumbromide with BuLi. Subsequent regioselective 9-BBN hydroboration followed by basic $H_2O_2$ oxidation delivered alcohol (**5.67**), in high yield (83%) (Scheme 5.26).



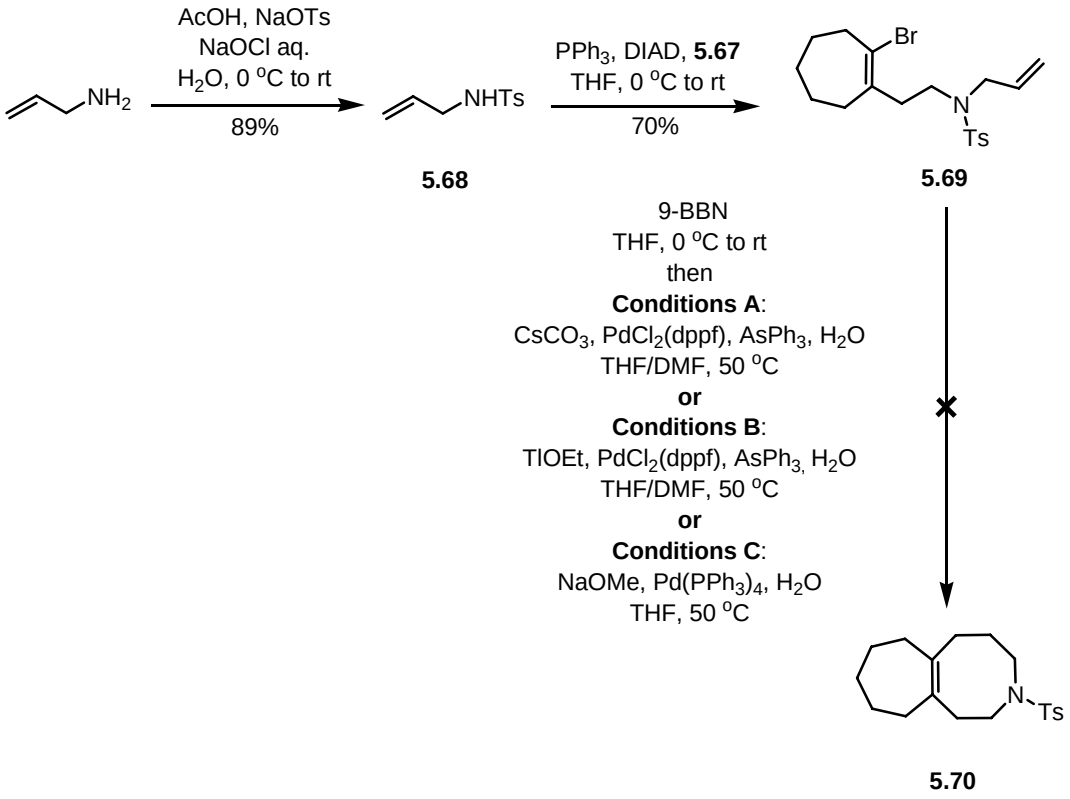

**5.65** **5.66** **5.67**

**Scheme 5.26** Preparation of bromoalcohol (**5.67**).

[5.64] The Vilsmeier salt $Me_2N^+$=CHBr·$Br^-$ is commercially available from Fluka, but it is fairly expensive and is not particularly shelf-stable, even when refrigerated.

[5.65] Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

The first route considered to access the [7,8]-bicyclic system explored the use of the intramolecular Suzuki-Miyaura cross-coupling reaction[5.66] of tosylamide (**5.69**), which was prepared in 70% *via* a Mitsunobu reaction between alcohol (**5.67**) and the *N*-allylsulfonamide (**5.68**).[5.67] Tosly amide (**5.69**) was subjected to sequential hydroboration/intramolecular B-alkly Suzuki cross coupling reaction. Various (high-dilution) conditions were tested for the cross-coupling step (Scheme 5.27).




**Scheme 5.27** (Attempted) preparation of diene (**5.70**).

In the first set of reaction conditions, the borane was slowly added to a diluted solution of $CsCO_3$, $PdCl_2$(dppf) and $AsPh_3$ in THF/DMF/$H_2O$. Under a second set of reaction conditions, the borane was treated with TlOEt and the resulting mixture was

[5.66] (a) Ref. 5.65. For selected reviews on the Suzuki-Miyaura cross-coupling see: (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.

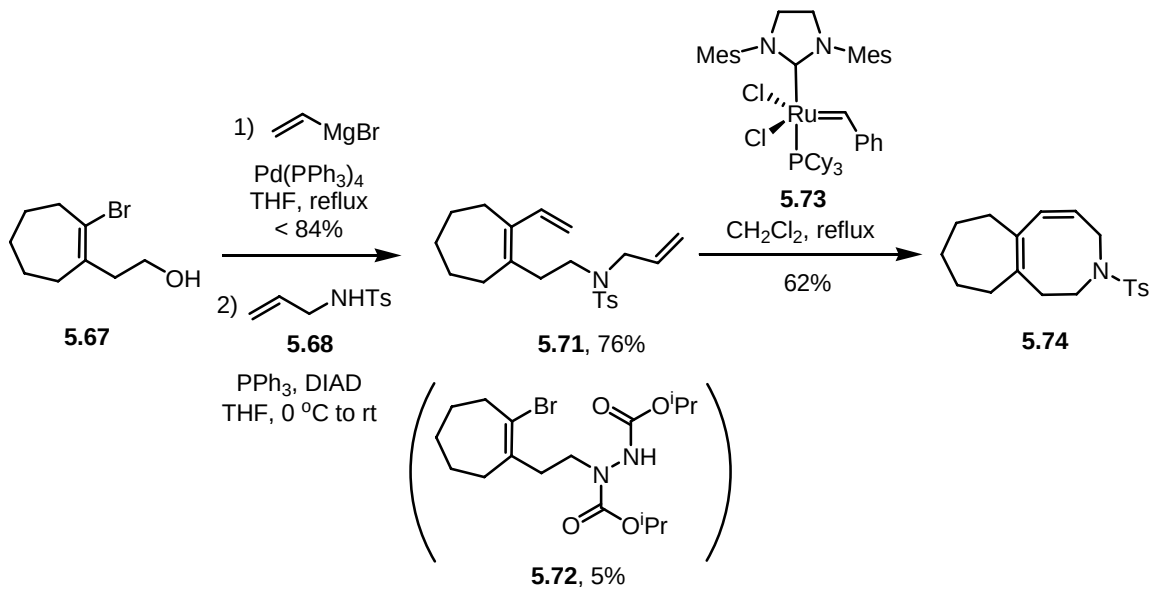
[5.67] For selected examples of intramolecular macrocyclization by means of a Suzuki-Miyaura reaction, see: (a) Kallan, N.; Halcomb, R. L. Org. Lett. **2000**, 2687. (b) Chemler, S. R.; Danishefsky, S. *J. Org. Lett.* **2000**, *2*, 2695.

added dropwise to a dilute solution of $Pd(dppf)Cl_2$ and $AsPh_3$ in $THF/DMF/H_2O$.[5.68] Finally, the cross-coupling reaction was carried out using the classical Suzuki reaction conditions, *i.e.*, $Pd(PPh_3)_4$ and NaOMe in $THF/H_2O$. Disappointingly, the desired bicyclic Ts-amide (**5.70**) was never formed.

The previous results were rationalized by arguing that the "folding" of the hydroborated side chain to reach the oxidatively-added palladium was entropically too demanding to take place in a system like (**5.69**). If so, this limitation could be overcome by moving the centers of reactivity away from the cycloheptene ring.

To test this hypothesis, triene (**5.71**) was prepared (Scheme 5.28). Using bromoalcohol (**5.67**) as the departure point, a Kumada-type cross coupling reaction with vinylmagnesiumbromide in the presence of catalytic $Pd(PPh_3)_4$ afforded the corresponding dieneol (not shown) in (less than) 84 % yield (contaminated with an inseparable impurity).[5.69] Interestingly, the analogous Stille coupling with tributylvinylstananne failed to produce the desired dieneol. Upon subjection to standard Mitsunobu reaction conditions ($PPh_3$, DIAD) with Ts-amide (**5.66**), the latter dienealcohol delivered the desired cycloheptene derivative (**5.71**) in good yield (76%), together with a small amount (approximately in 5% yield) of the hydrazocompound (**5.72**). Finally, triene (**5.71**) was subjected to the RCM reaction using the 2nd generation Grubbs catalyst (**5.73**). Under these conditions, the desired 1,3-diene (**5.74**) was produced in 62% yield clearly demonstrating the power of the RCM reaction in the preparation of difficult medium-sized ring systems. Thus, the feasibility in accessing the [7,8]-bicyclic system *via* the construction of the corresponding 8-membered ring was confirmed.

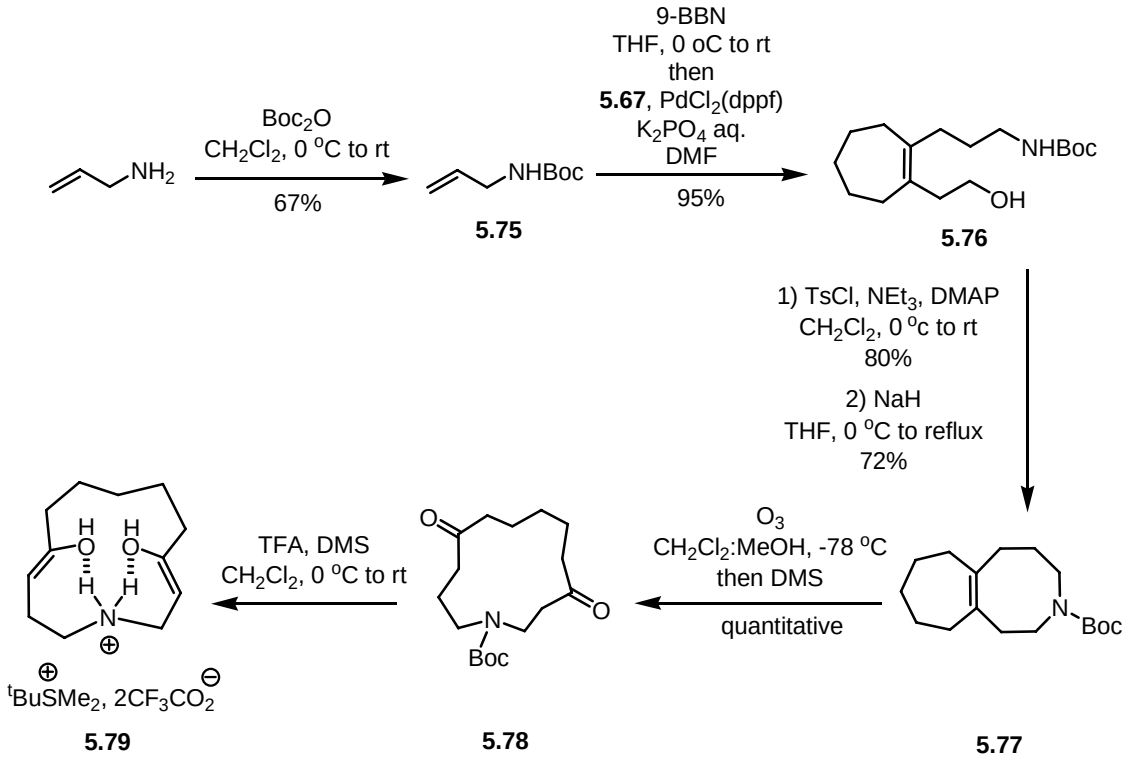
[5.68] For the use of TlOEt, see: Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691.
[5.69] For similar precedents see: (a) Carreno, M. C.; Urbano, A.; Di Vitta, C. *J. Org. Chem.* **1998**, *63*, 8320. (b) Atsuta, H.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 307.




**Scheme 5.28** Preparation of diene (**5.74**).

This encouraging result prompted us to test the preparation of the desired [7,8]-bicyclic amine (**5.64**) by means of an intramolecular $S_N2$-type reaction (Scheme 5.29). For this purpose, bromoalcohol (**5.67**) was subjected to a Suzuki-Miyaura cross coupling reaction with (hydroborated) *N*-Boc-allylamine (**5.75**) yielding alcohol (**5.76**) in 95%. The latter was tosylated under standard conditions (TsCl, $NEt_3$ and catalytic DMAP); upon treatment with NaH, the tosylate underwent an intramolecular displacement reaction producing the desired [7,8]-bicyclic system (**5.77**) in an impressive 72% yield.

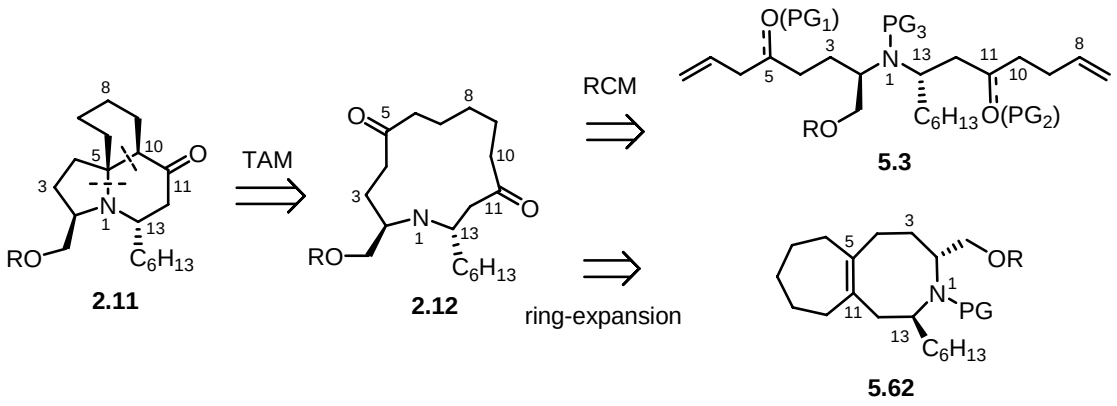
The ozonolysis of [7,8]-bicyclic (**5.77**), followed by reductive work-up with $SMe_2$ proceeded uneventfully affording the macrocyclic diketone (**5.78**) quantitatively. With this compound in hand, the proposed TAM reaction was attempted. The latter diketone (**5.78**) was treated with (excess) TFA in the presence of $SMe_2$. To our disappointment, at the time of this writing, only the dienol salt (**5.79**) has been isolated (Scheme 5.29).




**Scheme 5.29** Preparation of macrocyclic diketone (**5.78**) and its (attempted) TAM reaction.

# CHAPTER 6
# Concluding Remarks

A novel methodology, based on the hypothesis that the polycyclic framework of certain alkaloids can be accessed *via* a transannular Mannich (TAM) reaction of a conveniently functionalized macrocycle precursor, was investigated with respect to the total synthesis of the cylindricine alkaloids (**2.11**) (Scheme 6.1).

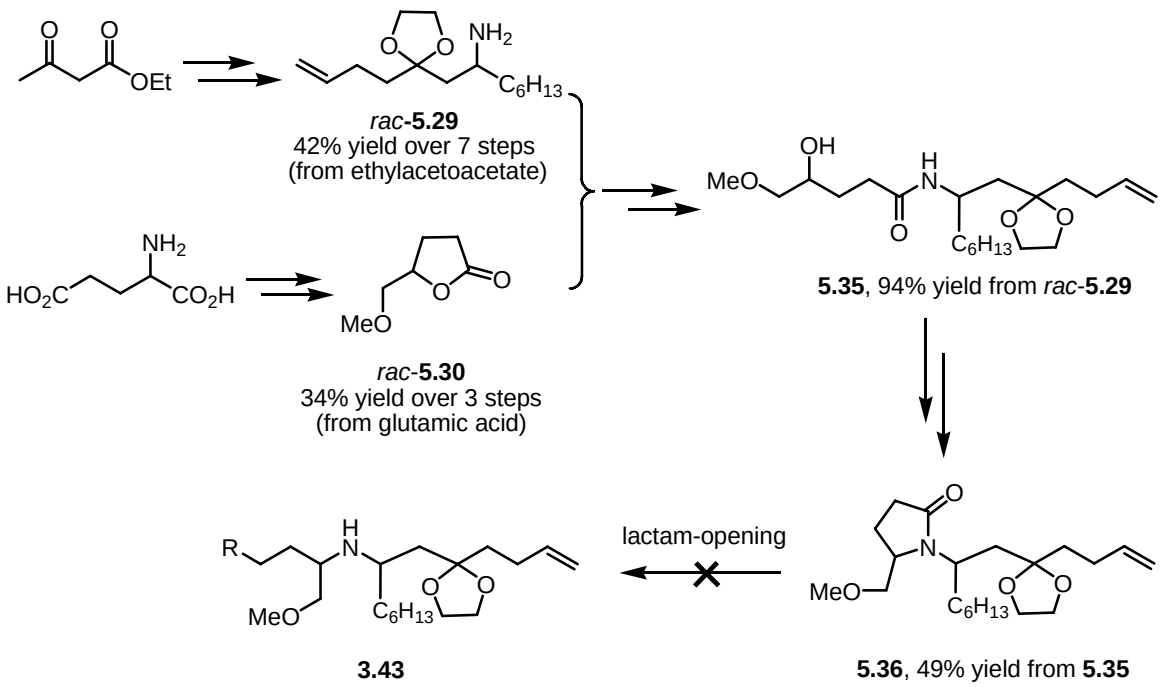



**Scheme 6.1** The proposed TAM reaction for accessing the cylindricines (**2.11**) and the approaches considered for preparing the key precursor, macrocycle (**2.12**).

The transition state (TS) for the TAM reaction was modeled using molecular mechanics (MM). Although the obtained predictions should be approached with care, moderate to excellent selectivities in favor of the desired cylindricines were predicted for the most trustworthy scenarios (late TS or early TS with "anti-Curtin-Hammett" conditions).

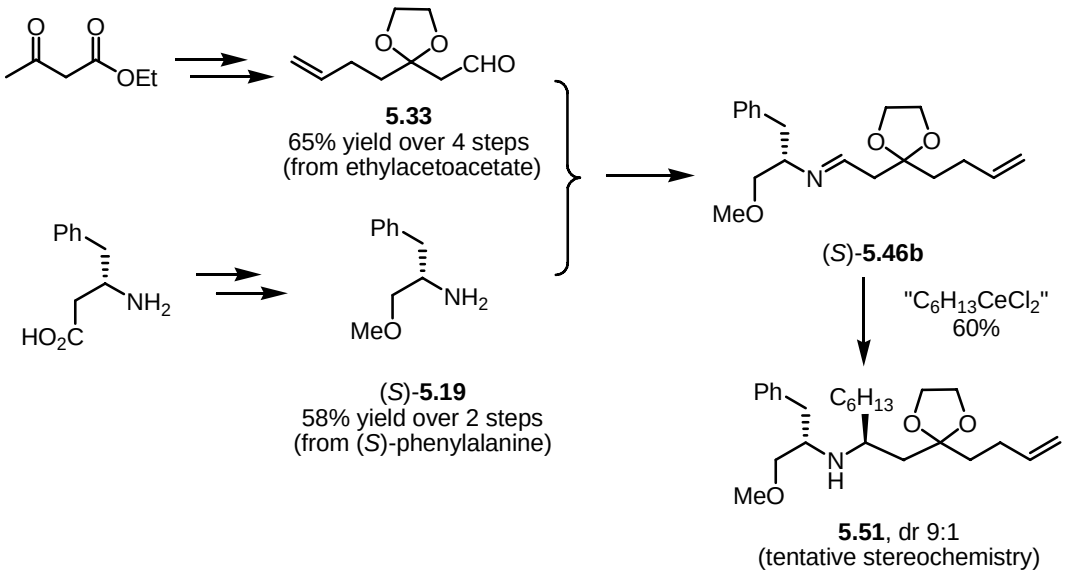
On the synthetic front, two general approaches for accessing the key macrocyclic precursor (**2.12**) were considered, namely the RCM of diene (**5.3**) and the ring-enlargement reaction of [7,8]-bicycle (**5.62**) (Scheme 6.1).

In one of the approaches investigated, lactam (**5.36**), a tentative advanced intermediary to diene (**5.3**), was prepared *via* the intramolecular aminocyclization of amide (**5.35**), which in turned was convergently obtained from the reaction of amine *rac*-(**5.29**) and lactone *rac*-(**5.30**). Unfortunately, and in spite of extensive experimentation, the opening of the lactam moiety in (**5.36**) did not proceed (Scheme 6.2).



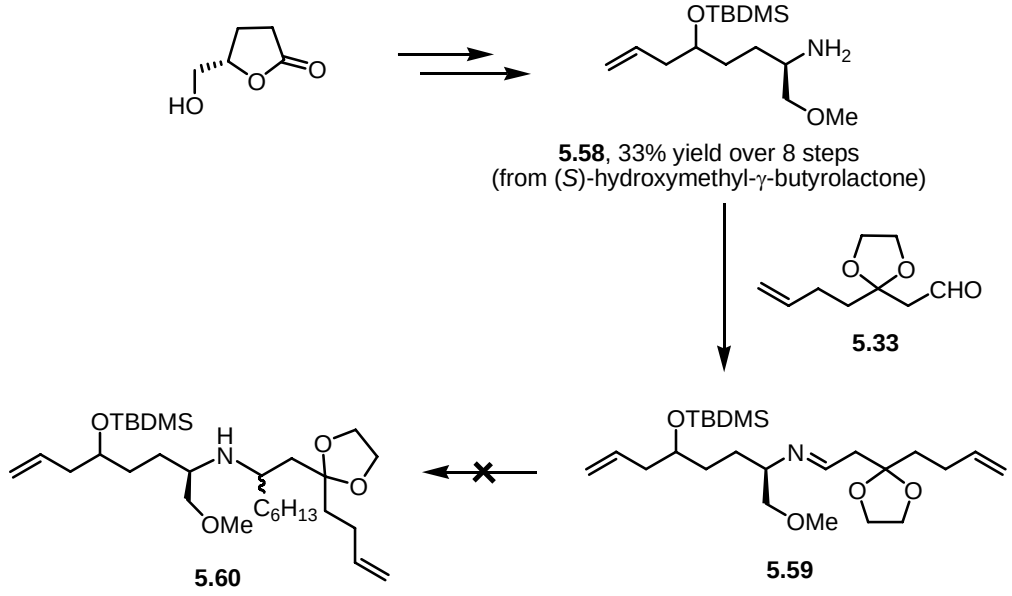

**Scheme 6.2** (Attempted) lactam-opening approach to diene (**5.3**).

Another synthetic route considered to access diene (**5.3**) explored the (stereoselective) addition of an organometallic reagent to the azamethine linkage of a chiral aldimine. During the various model studies performed, a particularly promising result was obtained when (model) aldimine (*S*)-(**5.46b**), prepared from amine (*S*)-(**5.19**) and aldehyde (**5.33**), was reacted with "hexylCeCl$_2$". Under these conditions, the addition product, amine (**5.51**), was delivered in good yield (60%) and with high diastereomeric ratio (9:1) (Scheme 6.3). Although no attempts were made to secure the stereochemical outcome of the reaction, it is likely, based on literature precedents, that the addition proceeded with chellation-control; thus, amine (**5.51**) has presumably been formed with the (*S*,*R*) configuration.



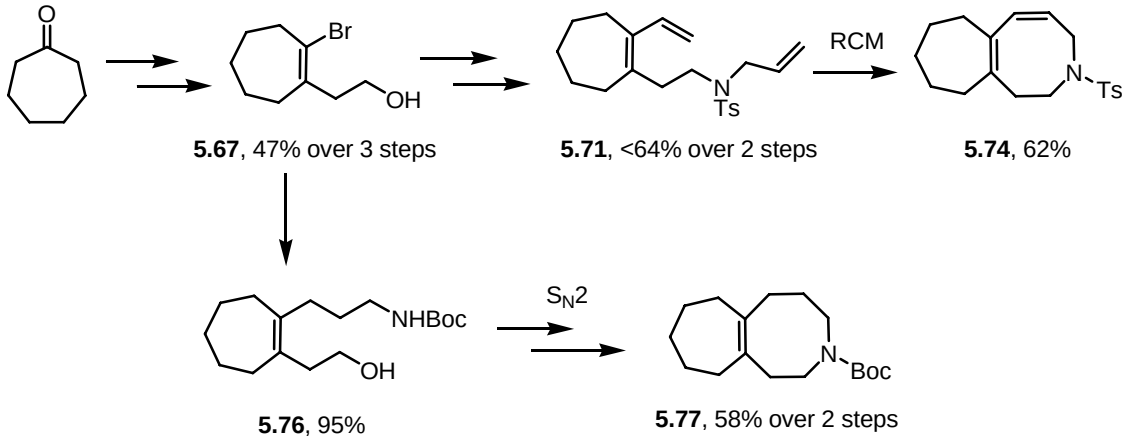

**Scheme 6.3** Model studies pertaining to the aldimine approach.

Disappointingly, when a similar strategy was attempted with aldimine (**5.59**), prepared by condensation of amine (**5.58**) with aldehyde (**5.33**), the expected amine (**5.60**) was not produced.



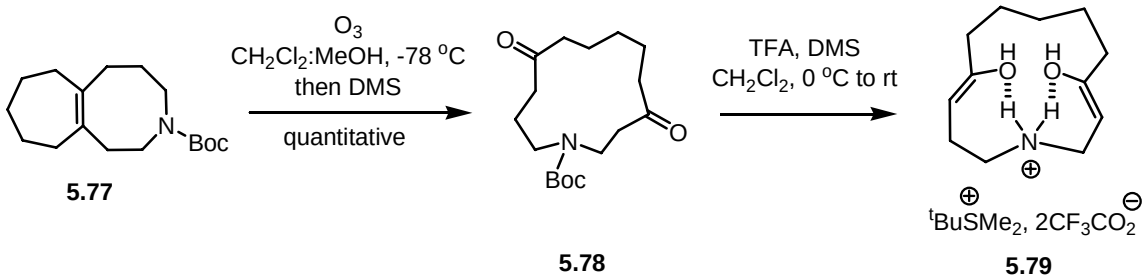

**Scheme 6.4** (Attempted) aldimine approach to diene (**5.3**).

Regarding the use of the ring-enlargement approach, it was found that the basic [7,8]-bicycle framework of (protected) amine (**5.62**), the planned precursor of key macrocycle (**2.12**), could be assembled through the formation of the corresponding 8-membered ring. Accordingly, the RCM reaction of triene (**5.71**),which was readily prepared from the key building block bromoalcohol (**5.67**), delivered diene (**5.74**) in 62% yield. Alternatively, and of greater interest, bicycle (**5.77**) was prepared by means of an intramolecular displacement reaction of the mesylated form of alcohol (**5.76**) (Scheme 6.5).




**Scheme 6.5** Model studies pertaining to the ring-enlargement approach.

The TAM reaction in model macrocycle diketone (**5.78**), obtained from (**5.77**) *via* oxidative cleavage of the central double bond, was (very) briefly tested. At the time of this writing, only the salt (**5.79**) has been isolated (Scheme 6.6). (Hypothetical) conditions that promote the desired TAM reaction are yet to be found and further studies are currently in progress.

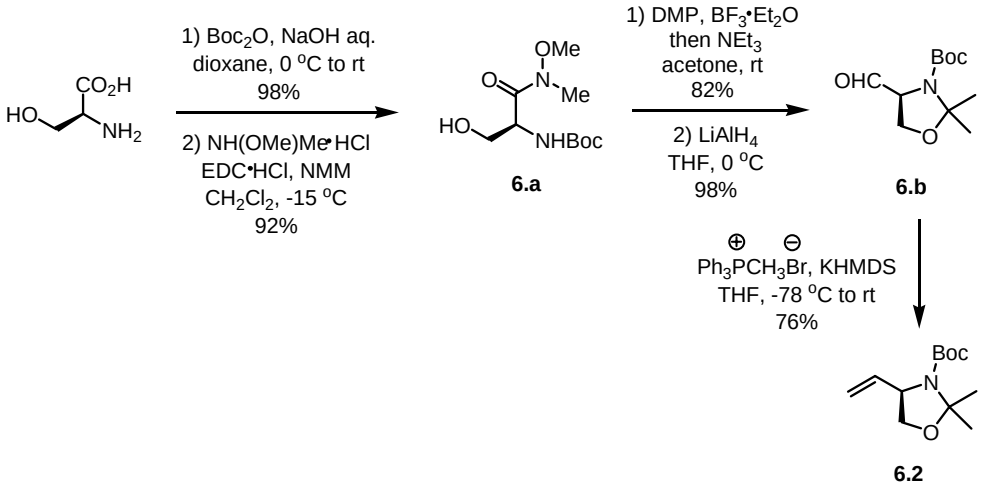



**Scheme 6.6** (Attempted) TAM reaction of macrocycle diketone (**5.78**).

Finally, it should be added that good progresses towards the preparation of the [7,8]-bicyclic amine (**5.62**) have already been accomplished. Thus, chiral cycloheptene derivatives (**6.3**) and (**6.2**), putative advanced intermediates in a highly convergent planned synthesis of (**5.62**), were obtained in high yields by means of a sequence that had as the key step the Suzuki-Miyaura cross coupling between cycloheptene alcohol (**6.1**) and known chiral oxazolidine (**6.2**) (Scheme 6.7).[6.1,6.2,6.3]

Regarding the (intramolecular) formation of the N1-C13 bond leading to the 8-memberd ring, the exact method to be used remains an open question at the time of this writing. Importantly, however, the high modular nature of the present approach allows the substrates for several different conceivable methods for this difficult transformation (*e.g.*, intramolecular reductive amination, Michael addition, Mitsunobu reaction, etc) to be prepared from the same building blocks.

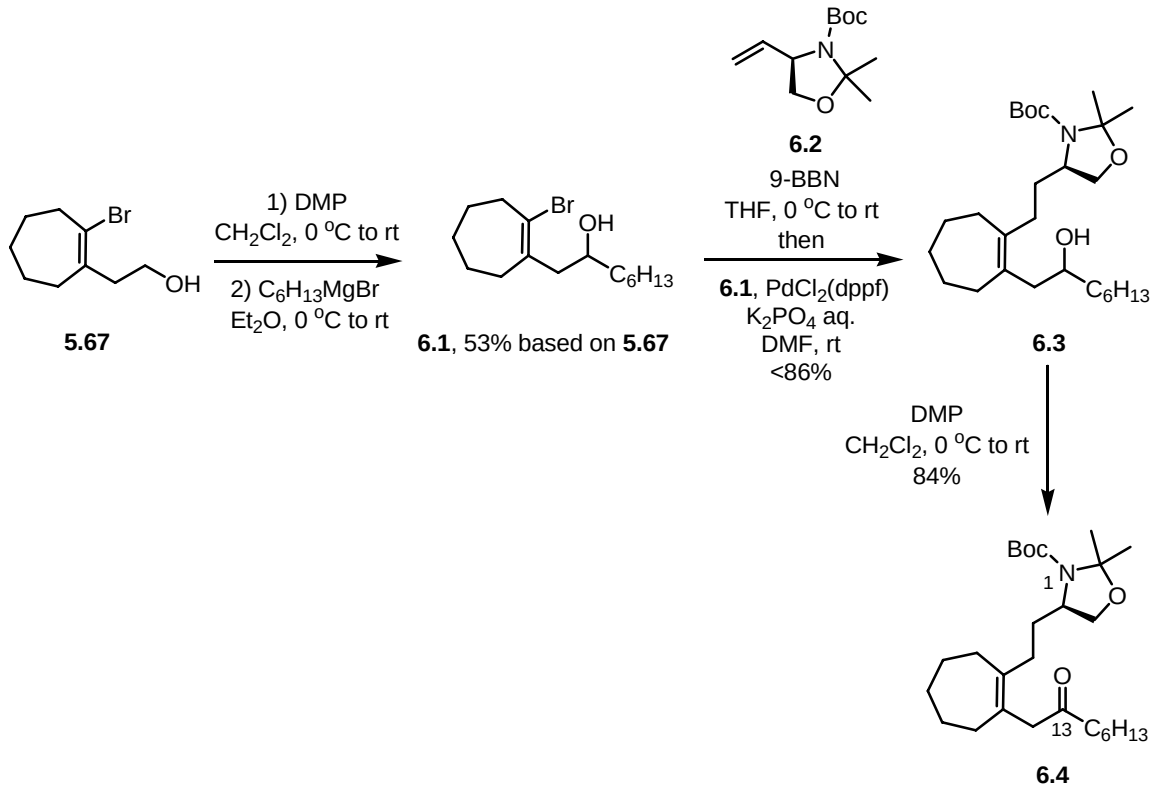
[6.1] The known chiral oxazolidine (**6.2**) was readily prepared from L-serine, in a sequence that has as the key intermediate the well known Garner aldehyde (**6.b**) (Scheme 6.A).[6.2,6.3]




**Scheme 6.A** Preparation of chiral oxazolidine (**6.2**).

[6.2] Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707.

[6.3] (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. (b) For a recent review on the Garner aldehyde, see: (b) Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans 1* **2001**, 2136.



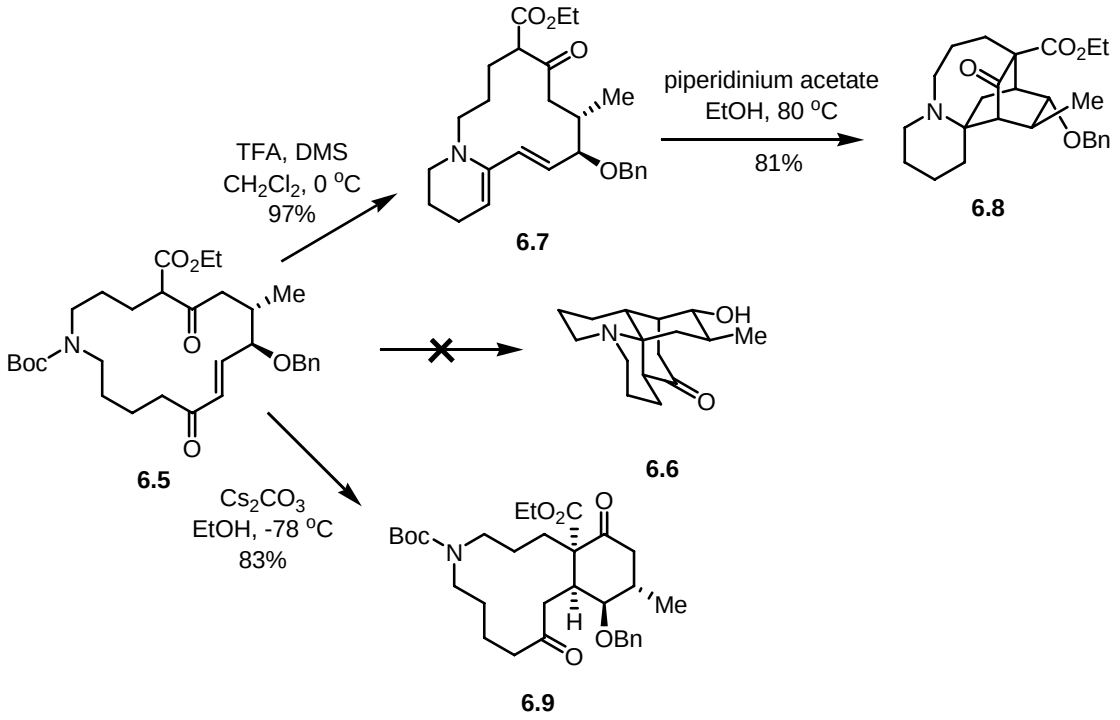

**Scheme 6.7** Preparation of cycloheptene alcohol (**6.3**) and ketone (**6.4**), putative advanced intermediates in a planned synthesis of **[**7,8]-bicyclic amine (**5.62**).

In conclusion, several strategies were investigated to prepare macrocycle diketone (**2.12**), the key intermediate that would allow testing if the framework of the cylindricine alkaloids could be accessed by means of a TAM reaction. Although the synthesis of (**2.12**) is yet to be achieved, good progresses have been made. The ring-enlargement approach, in particular, delivered very promising results in that macrocycle diketone (**5.78**), which contains the basic framework of (**5.12**) has been prepared. The TAM of (**5.78**) reaction is currently being studied. Furthermore, chiral cycloheptene derivatives (**6.3**) and (**6.4**), tentative intermediates in a planned synthesis of key macrocyclic diketone (**2.12**), have been prepared.

Finally, it is noted that while this work was in progress, Evans and Scheerer reported on the attempted total synthesis of clavolonine (**6.6**) from the macrocyclic amine (**6.5**) using the same TAM reaction concept.[6.4] Although several conditions were investigated, the desired alkaloid (**6.6**) was never formed; instead a range of different

[6.4] Evans, D. A.; Scheerer, J. R. *Angew. Chem. Int. Ed.* **2005**, *44*, 6038.

products, compounds (**6.7**) to (**6.9**), resulting from various others transannular processes, were isolated (Scheme 6.8).




**Scheme 6.8** Transannular reactions of macrocyclic amine (**6.5**).

# CHAPTER 7
# Experimental

## 7.1 - General

All moisture- and air- sensitive reactions were carried out under an argon atmosphere using oven-dried or flame-dried glassware. $Et_2O$, THF and toluene were distilled under nitrogen from sodium-benzophenone. $CH_2Cl_2$, $NEt_3$, pyridine and $^iPr_2NH$ were distilled under nitrogen from $CaH_2$. Anhydrous DMSO and DMF were purchased from Aldrich and stored over 4Å MS under argon. $^1$H-NMR (200 MHz, 300 MHz) and $^{13}$C-NMR (75 MHz) spectra were recorded on either a Bruker AC-200 (200 MHz) or a Varian Mercury 300 (300 MHz) spectrometers at ambient temperature. Chemical shifts (δ) are reported in ppm. Undeuterated solvents residues were used as internal standard (for $CHCl_3$, $^1$H: 7.27 ppm and $^{13}$C: 77.0 ppm). Coupling constants (*J*) are given in Hertz (Hz).[1] Multiplicities of peaks are reported in the following way: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ´t´ (pseudo-triplet), ´q´(pseudo-quartet) and combinations of these. (Note: for $^1$H (200 MHz) no coupling constants are reported). Optical rotations were measured with a Perkin Elmer 241 Polarimeter at ambient temperature and the concentration (*c*) is given in g *per* 100 mL. Electron impact (EI) low resolution mass spectra (LRMS) were performed with a VG Trio-2 single quadropole instrument at the Department of Chemistry, Technical University of Denmark. Melting points of crystalline materials were determined on a Heidolph capillary melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) analyses were performed using 0.25 mm Merk Kiselgel aluminum-backed 60 $F_{254}$ silica gel plates. Visualization was achieved by using (some of) the following sequential steps: i) exposure to UV light, ii) brief exposure to iodine vapors, iii) deeping on a solution of either 5-10% of phosphormolybdic acid in EtOH, basic $KnMnO_4$ or ninydridin and iv) gentle heating. Merk silica gel 60 (40-63 μm, 230-400 mesh) was used for flash chromatography purification. Known compounds were characterized by $^1$H- and/or $^{13}$C-NMR. New compounds are typically characterized by $^1$H- and $^{13}$C-NMR. Molecular sieves were dried at 150-160 $^o$C for at least 12 h and then allowed to reach room temperature under argon. Unless otherwise stated, commercially available reagents, purchased from Aldrich, Fluka, Merk or TCI were used without further purification. “Aqueous ½ saturated brine” and “aqueous 1/3 saturated $NaHCO_3$” refer to a water:brine, 1:1

[7.1] For $^1$H-NMR (200 MHz) spectra no coupling constants are reported.

(v:v) and water:saturated $NaHCO_3$, 2:1 (v:v) solutions, respectively. The following cooling baths were used: dry ice slurried in acetone (approximately -78 $^oC$). Commercial NaH (as a 55-60% dispersion in oil) was washed with pentane (2 portions that cover the amount of NaH dispersion used) and the last traces of pentane are removed under high vacuum.

## 7.2 – General Experimental Procedures

**Procedure for the preparation of demetallated silica gel**:
Silica gel (1 Kg) was slurried in aqueous 10% HCl (2 L). The resulting yellow aqueous phase was decanted off and the remaining silica gel was washed with 1 L batches of distilled water until the washings reached pH 4 (typically 15-20 washes are required). The obtained silica gel was then treated with a solution of aqueous 25% ammonia (1 mL) in water (1 L). The aqueous phase was decanted off and the remaining silica gel was oven-dried at 160 $^oC$ for 2 days with occasional manual stirring.

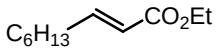
$Pd(PPh_3)_4$ **Tetrakis(triphenylphosphine)palladium**

Following a literature procedure,[7.2] a vigorously stirred yellow suspension of $PdCl_2$ (500 mg, 2.8 mmol, 1.0 eq.), $PPh_3$ (3.70 g, 14.1 mmol, 5.0 eq.) in dry DMSO (previously degassed by bubbling argon for approximately ½ h) was inserted in an oil bath previously heated to 150 $^oC$. After 10-15 min. at this temperature, an orange solution is obtained. The oil bath was then removed and $N_2H_4 \cdot H_2O$ (565 mg, 11.3 mmol, 4 eq.) was immediately added dropwise with vigorous gas evolution observed. After addition, the mixture was allowed to slowly reach room temperature. An initial transient black color faded away into a golden and then into a bright yellow coloration. After 5-10 min., some crystals started forming. The stirring was stopped, the reaction flask was covered with silver foil and this mixture was left to rest at room temperature under argon overnight. The obtained mixture was filtered and the resulting crystals were rinsed with cold EtOH (2 portions of 35 mL) and cold $Et_2O$ (3 portions of 15 mL). The title compound was obtained as bright yellow crystals (3.0 g, 92%) which were best kept refrigerated, under argon and protected from light. Mp 116-118 $^oC$ (lit. 116 $^oC$).

[7.2] Komiya, S. In "Synthesis of Organometallic Compounds: A Practical Guide" **1997**, Wiley, New York.

**Preparation of anhydrous $CeCl_3$**:
Stirred powdered $CeCl_3 \cdot 7H_2O$ was slowly heated to 140 °C over 3½ h under vacuum (0.5 mm), kept at these conditions overnight and allowed to reach room temperature under an argon atmosphere.

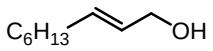
## 7.3 – Preparation of Compounds



**(*E*)-Ethyl non-2-enoate**

Following a literature procedure,[7.3] a biphasic system of $K_2CO_3$ (8.3 g, 60 mmol, 2.0 eq.), $H_2O$ (6 mL), triethylphosphonoacetate (8.1 g, 36 mmol, 1.2 eq.) and heptaldehyde (3.4 g, 30 mmol, 1.0 eq.) was stirred vigorously for 20 h at room temperature under an argon atmosphere. $H_2O$ (15 mL) was then added and the mixture was carefully decanted. The solid residue was washed with hexane (3 portions of 10 mL). After separation of the layers, the aqueous layer was extracted with hexane (3 portions of 10 mL). The combined organic layers were dried ($MgSO_4$), the solvent evaporated affording a colorless oil. Purification by reduced-pressure distillation (56-59 °C, 0.4 mm) afforded the title compound as a colorless oil (5.3 g, 95%).

$R_f$ (hexane: EtOAc, 4:1 (v:v)) 0.53; $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 167.0, 149.6, 121.5, 60.3, 32.4, 31.8, 29.0, 28.2, 22.8, 14.5, 14.3.



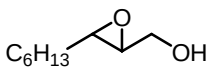
**(*E*)-2-Nonen-1-ol** (**5.8**)

To a -78 °C cold solution of the (*E*)-ethyl non-2-enoate (2.5 g, 13.6 mmol, 1.0 eq.) in $CH_2Cl_2$ (50 mL) was dropwise added a solution of Dibal in toluene (30 mL, 35.3 mmol, 2.6 eq.). The obtained solution was stirred at this temperature for 2½h, after which MeOH (15 mL) was carefully added. After vigorous stirring for 5-10 min. at room temperature, a gel-like biphasic system formed. A saturated aqueous solution of Rochelle's salt (50 mL) was then added and the resulting mixture was stirred at room temperature until a clear biphasic system was obtained (approximately 2 h). The layers were separated and the aqueous layer was further extracted with $CH_2Cl_2$ (2 portions of 15 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent under vacuum followed by purification by

[7.3] Villieras, J.; Rambaud, M. *Synthesis* **1983**, 300.

distillation at reduced pressure (Vigreaux) (45-47 ºC, 0.3 mm; lit.[6.4] 102-104 ºC, 12 mm.) delivered the known (*E*)-allylic alcohol (**5.8**) (1.5 g, 79%).

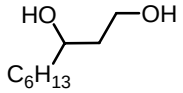
$R_f$ (hexane: EtOAc, 4:1 (v:v)) 0.25; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 5.61 (m, 2H), 4.05 (d, 2H), 1.95 (q, 3H), 1.15-1.40 (m, 8H), 0.85 (t, 3H).




**(*E*)-2,3-epoxy-1-nonanol**

Following a literature procedure,[7.5] (*E*)-2-nonen-1-ol (**5.8**) (1.4 g, 10 mmol, 1.0 eq.) and MCPBA (83%, 2.69 g, 13 mmol, 1.3 eq.) were stirred in $CH_2Cl_2$ (41 mL) for ca. 3 h at room temperature, after which the reaction mixture was washed thoroughly with saturated $Na_2CO_3$ aqueous solution (3 portions of 30 mL) and brine (3 portions of 30 mL). The organic layer was dried ($Na_2SO_4$), and the solvent removed under vacuum to afford the title compound as a white solid which appeared as white needles after recrystallisation from (hot) hexane(1.5 g, 95%).

$R_f$ (hexane: EtOAc, 4:1 (v:v)) 0.1; $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 62.0, 58.7, 56.3, 31.9, 31.8, 29.3, 26.1, 22.8, 14.3.




**Nonane-1,3-diol (5.9)**

Following a literature procedure,[7.5] (*E*)-2,3-epoxy-1-nonanol (8.4 g, 53.5 mmol, 1.0 eq.) was dissolved in THF (85 mL) and the obtained solution cooled to -30 ºC (dry ice/$CCl_4$ bath). A solution of Red-Al (3.5 M in toluene, 46 mL, 3 eq.) was dropwise added and the reaction mixture obtained was stored at -10 ºC for 2 days under an argon .atmosphere. The reaction was allowed to reach ice bath temperature, carefully quenched with $H_2O$ (150 mL) and extracted well with ether (5 portions of 200 mL). The combined organic layers were washed with brine (250 mL), dried ($Na_2SO_4$) and the solvent removed under vacuum. Vigreaux distillation at reduced pressure (92-94 ºC, 0.8 mm (lit.[7.5] 104-105 ºC, 1 mm)) afforded the title compound as a colorless oil (6.6 g, 77%).

$R_f$ (hexane: EtOAc, 1:1 (v:v)) 0.2; $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 72.5, 62.0, 38.5, 38.1, 32.0, 29.5, 25.7, 22.8, 14.3.

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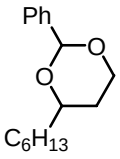
[7.4] Kitiching, W.; Lewis, J. A.; Perkins, M. V.; Drew, R.; Moore, C. J.; Schurig, V.; König, W. A.; Francke, W. *J. Org. Chem. Soc.* **1989**, *54*, 3893.

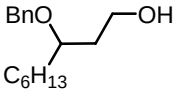
[7.5] Kitching, W.; Lewis, J. A.; Perkins, M. V.; Drew, R.; Moore, C. J.; Schurig, V.; König, W. A.; Francke, W. *J. Org. Chem.* **1989**, *54*, 3893.



**4-Hexyl-2-phenyl-1,3-dioxane (5.11)**

A mixture of nonane-1,3-diol (**5.9**) (500 mg, 3.1 mmol, 1.0 eq.), benzaldehyde (497 mg, 4.7 mmol, 1.5 eq.) and approximately 5 drops of concentrated $H_2SO_4$ in dry DMSO (13 mL) was stirred at room temperature under argon for 3 days, after which 4 Å MS (approximately 0.5 g) were added and stirring continued for further 2 days. The mixture was then carefully decanted and the MS were washed with DMSO (2 portions of 4 mL). $H_2O$ (200 mL) was added to the combined organic layers and this mixture extracted with $Et_2O$ (3 portions of 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to afford a yellow oil. Purification by flash chromatography (hexane:EtOAc, 4:1 (v:v)) afforded the title compound as faint yellow oil (0.58 g, 75%).

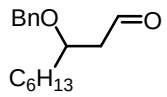
$R_f$ (hexane: EtOAc, 1:1 (v:v)) 0.73; $^1$H-NMR (*d*-DMSO, 200 MHz) δ 7.30-7.42 (m, 5H), 5.42 (s, 1H), 4.10 (dd, 1H), 3.85 (dd, 1H), 3.75-3.82 (m, 1H), 1.20-1.60 (m, 12H), 0.83 (t, 3H); $^{13}$C-NMR (*d*-DMSO, 75 MHz) δ 139.8, 129.1, 128.6, 126.7, 101.0, 77.0, 67.0, 36.2, 31.9, 31.7, 29.4, 25.1, 22.8, 14.6.



**3-(Benzyloxy)nonan-1-ol (5.11)**

To a solution of 4-hexyl-2-phenyl-1,3-dioxane (**5.10**) (565 mg, 2.3 mmol, 1.0 eq.) in $CH_2Cl_2$ (23 mL) at -60 $^o$C was dropwise added over 15 min. a solution of Dibal in $CH_2Cl_2$ (1 M, 6.8 mL, 3 eq.). The obtained solution was allowed to reach room temperature slowly over 3 h, after which time it was cooled to ice bath temperature and carefully quenched with aqueous 1 M HCl (8 mL). The resulting mixture was stirred at room temperature until a biphasic system could distinctively be seen (approximately ½ h), and then partitioned between $H_2O$ (100 mL) and EtOAc (100 mL). The aqueous layer was further extracted with EtOAc (100 mL) and the combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (80 mL), brine (80 mL) and dried ($Na_2SO_4$).Removal of the solvent under vacuum afforded alcohol (**5.12**) (564 mg, 98%) as colorless oil which typically was used directly in subsequent reactions.

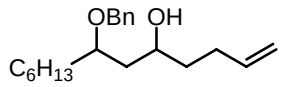
$R_f$ (hexane: EtOAc, 1:1 (v:v)) 0.52; $^1$H-NMR (*d*-DMSO, 200 MHz) δ 7.25-7.33 (m, 5H), 4.42 (s, 2H), 4.35 (t, 1H), 3.5 (´q´, 3H), 1.52-1.71 (m, 2H), 1.40-1.50(m, 2H), 1.19-1.35 (m, 8H), 0.81 (t, 3H); $^{13}$C-NMR (*d*-DMSO, 75 MHz) δ 139.9, 128.8, 128.1, 127.8, 76.4, 70.6, 58.3, 39.4, 37.8, 34.2, 32.0, 29.6, 25.3, 22.8.



**3-(Benzyloxy)nonanal**

To a 0 °C cold suspension of DMP (1.1 g, 2.6 mmol, 1.2 eq.) in $CH_2Cl_2$ (10.5 mL) was dropwise added a solution of 3-(benzyloxy)nonan-1-ol (**5.11**) (522 mg, 2.1 mmol, 1.0 eq.) in $CH_2Cl_2$ (9 mL). The resulting mixture was stirred at ice bath temperature for ½ h, allowed to reach room temperature and stirred for 1 h further. The reaction was then quenched by addition of 10% $Na_2S_2O_3$ aqueous solution (15 mL) and $NaHCO_3$ aqueous solution (44 mL) and stirred until an homogenous biphasic system was obtained (approximately 20 min.). After separation of the layers, the aqueous layer was extracted with EtOAc (2 portions of 30 mL); the combined organic layers were washed with brine (60 mL), dried ($Na_2SO_4$) and the solvent removed under vacuum to afford the title compound as a pale yellow oil (505 mg, 97%), which was used without further purification.

$R_f$ (hexane: EtOAc, 1:1 (v:v)) 0.70; $^1$H-NMR (*d*-DMSO, 200 MHz) δ 9.68 (s, 1H), 7.21-7.38 (m, 5H), 4.50 (s, 2H), 3.92 (quint, 1H), 2.97 (d, 2H), 1.39-1.62 (m, 2H), 1.13-1.36 (m, 8), 0.83 (t, 3H); $^{13}$C-NMR (*d*-DMSO, 75 MHz) δ 203.2, 139.4, 128.8, 128.2, 128.0, 74.4, 70.6, 48.4, 34.3, 31.9, 29.4, 25.2, 22.7, 14.6.



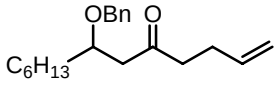
**7-(Benzyloxy)tridec-1-en-5-ol (5.13)**

i) Preparation of the Grignard reagent (**5.12**): A solution of 4-bromobutene (511 mg, 3.8 mmol, 2.5 eq.) in $Et_2O$ (2.7 mL) was dropwise added at room temperature under an argon atmosphere to a stirred mixture of Mg turnings (198 mg, 8.2 mmol, 5.0 eq.; activated by the addition of a crystal of $I_2$) in $Et_2O$ (5 mL). Dropwise addition was regulated to maintain a gentle reflux. After the alkyl bromide addition was completed, the mixture was stirred an additional ½ h at room temperature.

ii) Preparation of 7-(benzyloxy)tridec-1-en-5-ol (**5.13**):To a chilled (0 °C) mixture of 3-(benzyloxy)nonanal (0.37 g, 1.5 mmol, 1.0 eq.) in $Et_2O$ (7 mL) was dropwise added the above (decanted) Grignard solution. After addition, the mixture was stirred at room temperature for 1½ h, refluxed for 15 min., re-cooled to ice bath temperature and quenched by the careful addition of saturated $NH_4Cl$ aqueous solution (7 mL). The reaction mixture was partitioned between EtOAc (100 mL) and $H_2O$ (100 mL) and the aqueous layer was extracted with EtOAc (2 portions of 25 mL). The combined organic layers were washed with ½ saturated $NaHCO_3$ aqueous solution (80 mL), brine (80 mL), dried ($MgSO_4$) and the solvent was removed under reduced

pressure. Purification by flash chromatography (hexane:EtOAc, 2:1 (v:v)) delivered the title compound as a pale yellow oil (361 mg, 79%).

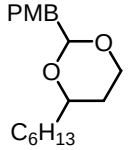
$R_f$ (hexane: EtOAc, 2:1 (v:v)) 0.56; $^1$H-NMR (*d*-DMSO, 200 MHz) δ 7.20-7.38 (m, 5H), 5.78 (m, 1H), 4.94 (´d´, 1H), 4.85 (´d´, 1H), 4.43 (d, 1H), 4.40 (s, 1H), 4.25 (dd, 1H), 3.56-63 (m, 1H), 3.46-3.55 (m, 1H), 1.90-2.18 (m, 2H), 1.15-1.56 (m, 14H), 0.83 (t, 3H); $^{13}$C-NMR (*d*-DMSO, 75 MHz) (selection) δ 141.3, 140.0, 128.8, 128.2, 128.0, 115.1, 76.7, 69.1, 43.0, 37.8, 34.2, 32.0, 29.6, 25.3, 29.5, 22.8, 14.6.




**7-(Benzyloxy)tridec-1-en-5-one (5.15)**

To a 0 °C cold suspension of DMP (310 mg, 0.73 mmol, 1.4 eq.) in $CH_2Cl_2$ (2.9 mL) was dropwise added a solution of **7**-(benzyloxy)tridec-1-en-5-ol (**5.14**) (161 mg, 0.53 mmol, 1.0 eq.) in $CH_2Cl_2$ (2.5 mL). The resulting mixture was stirred at ice bath temperature for ½ h, allowed to reach room temperature and stirred for 1 h further. The reaction was then quenched by addition of 10% $Na_2S_2O_3$ aqueous solution (5 mL) and $NaHCO_3$ aqueous solution (15 mL) and stirred until an homogenous biphasic system was obtained (approximately 20 min.). After separation of the layers, the aqueous layer was extracted with EtOAc (2 portions of 15 mL); the combined organic layers were washed with brine (40 mL), dried ($Na_2SO_4$) and the solvent removed under vacuum to afford the title compound as a pale yellow oil (160 mg, quantitative), which was used without further purification.

$R_f$ (hexane: EtOAc, 2:1 (v:v)) 0.71; $^1$H-NMR (*d*-DMSO, 200 MHz) δ 7.20-7.37 (m, 5H), 5.75 (m, 1H), 4.96 (´d´, 1H), 4.80 (´d´, 1H), 4.40 (s, 2H), 3.80 (quint., 1H), 2.65 (dd, 1H), 2.45-2.60 (m, 3H), 2.18 (q, 2H), 1.15-1.56 (m, 10H), 0.83 (t, 3H); $^{13}$C-NMR (*d*-DMSO, 75 MHz) δ 209.3, 138.4, 128.8, 128.5, 127.9, 126.2, 114.3, 75.4, 72.4, 47.5, 43.6, 34.8, 32.5, 31.0, 30.4, 22,4, 22.3, 14.4.

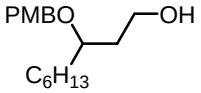



**4-Hexyl-2-(4-methoxybenzyl)-1,3-dioxane (5.18)**

A solution of nonane-1,3-diol (**5.9**) (500 mg, 3.1 mmol, 1.0 eq.), anisaldehyde dimethyl acetal (710 mg, 3.9 mmol, 1.25 eq.) and CSA (29 mg, 0.13 mmol, 4 mol% with respect to the diol) in DMF (20 mL) is stirred at 60 °C under house vacuum. After reaching room temperature, the resulting solution was partitioned between $H_2O$ (250 mL) and $Et_2O$ (120 mL). The aqueous layer was extracted with $Et_2O$ (2 portions of 50 mL). The combined organic layers were washed with brine (100 mL), dried ($Na_2SO_4$) and the solvent removed under vacuum.

Purification by flash chromatography (hexane:EtOAc, 2:1 (v:v)) delivered the title compound as a colorless oil (850 mg, 97%).

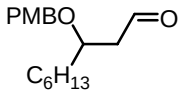
$R_f$ (hexane: EtOAc, 2:1 (v:v)) 0.55; $^1$H-NMR (*d*-DMSO, 200 MHz) δ 7.33 (d, 2H), 6.84 (d, 2H), 5.40 (s, 1H), 4.13 (dd, 1H), 3.63-3.9 (m, 5H), 1.21-1.58 (m, 12H), 0.82 (t, 3H); $^{13}$C-NMR (*d*-DMSO, 75 MHz) δ 159.9, 132.3, 127.9, 113.9, 100.9, 77.0, 66.9, 55.8, 36.3, 32.0, 31.6, 29.4, 25.1, 22.8, 14.6.




**3-(4-Methoxybenzyloxy)nonan-1-ol**

To a solution of 4-hexyl-2-(4-methoxybenzyl)-1,3-dioxane (**5.18**) (480 mg, 1.7 mmol, 1.0 eq.) in $CH_2Cl_2$ (17 mL) at -60 °C was dropwise added over 15 min. a solution of Dibal in $CH_2Cl_2$ (1 M, 4.3 mL, 2.5 eq.). The obtained solution was allowed to reach room temperature slowly over 3½ h, after which time it was cooled to ice bath temperature and carefully quenched with aqueous 1 M HCl (6 mL). The resulting mixture was stirred at room temperature until a biphasic system could distinctively be seen (approximately ½ h), and then partitioned between $H_2O$ (100 mL) and EtOAc (100 mL). The aqueous layer was further extracted with EtOAc (100 mL) and the combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (80 mL), brine (80 mL) and dried ($Na_2SO_4$).Removal of the solvent under vacuum afforded alcohol (**5.12**) (486 mg, quantitative) as a colorless oil which typically was used directly in the reaction.

$R_f$ (hexane: EtOAc, 1:1 (v:v)) 0.39; $^1$H-NMR (*d*-DMSO, 200 MHz) δ 7.21 (d, 2H), 6.83 (d, 2H), 4.38 (s, 2H), 4.30 (t, 1H), 3.67 (s, 3H), 3.45 (q, 3H), 1.50-1.63 (m, 2H), 1.36-1.48 (m, 2H), 1.21-1.32 (m, 8H), 0.80 (t, 3H); $^{13}$C-NMR (*d*-DMSO, 75 MHz) (selection) δ 159.2, 131.9, 129.7, 114.2, 76.0, 70.3, 58.3, 55.7, 37.8, 34.3, 32.0, 29.6, 25.3, 22.8, 14.6.

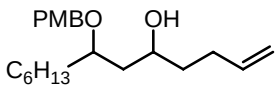



**3-(4-Methoxybenzyloxy)nonanal**

To a 0 °C cold suspension of DMP (929 mg, 2.2 mmol, 1.3 eq.) in $CH_2Cl_2$ (9 mL) was dropwise added a solution of 3-(4-methoxybenzyloxy)nonan-1-ol (486 mg, 1.7 mmol, 1.0 eq.) in $CH_2Cl_2$ (7 mL). The resulting mixture was stirred at ice bath temperature for ½ h, allowed to reach room temperature and stirred for 1 h further. The reaction was then quenched by addition of 10% $Na_2S_2O_3$ aqueous solution (15 mL) and $NaHCO_3$ aqueous solution (44 mL) and stirred until an homogenous biphasic system was obtained (approximately 20 min.). After separation

of the layers, the aqueous layer was extracted with EtOAc (2 portions of 30 mL); the combined organic layers were washed with brine (60 mL), dried ($Na_2SO_4$) and the solvent removed under vacuum to afford the title compound as a pale yellow oil (450 mg, 95%), which was used without further purification.

$R_f$ (hexane: EtOAc, 1:1 (v:v)) 0.61; $^1$H-NMR (*d*-DMSO, 200 MHz) δ 9.63 (s, 1H), 7.20 (d, 2H), 6.83 (d, 2H), 4.40 (s, 2H), 3.85 (quint., 1H), 3.73 (s, 3H), 2.51-2.54 (m, 2H), 1.41-1.60 (m, 2H), 1.20-1.35 (m, 8H), 0.82 (t, 3H); $^{13}$C-NMR (*d*-DMSO, 75 MHz) δ 203.2, 159.3, 131.3, 129.9, 114.3, 74.0, 70.3, 55.7, 48.4, 34.3, 31.9, 29.4, 25.2, 22.7, 14.6.



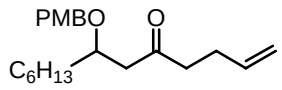

**7-(4-Methoxybenzyloxy)tridec-1-en-5-ol**

i) Preparation of the Grignard reagent (**5.12**): A solution of 4-bromobutene (530 mg, 3.9 mmol, 2.5 eq.) in $Et_2O$ (2.7 mL) was dropwise added at room temperature under an argon atmosphere to a stirred mixture of Mg turnings (191 mg, 7.9 mmol, 4.9 eq.; activated by the addition of a crystal of $I_2$) in $Et_2O$ (5 mL). Dropwise addition was regulated to maintain a gentle reflux. After the alkyl bromide addition was completed, the mixture was stirred an additional ½ h at room temperature.

ii) Preparation of 7-(4-methoxybenzyloxy)tridec-1-en-5-ol: To a chilled (0 $^o$C) mixture of 3-(4-methoxybenzyloxy)nonanal (440 g, 1.6 mmol, 1.0 eq.) in $Et_2O$ (7 mL) was dropwise added the above (decanted) Grignard solution. After addition, the mixture was stirred at room temperature for 1½ h, refluxed for 15 min., re-cooled to ice bath temperature and quenched by the careful addition of saturated $NH_4Cl$ aqueous solution (7 mL). The reaction mixture was partitioned between EtOAc (100 mL) and $H_2O$ (100 mL) and the aqueous layer was extracted with EtOAc (2 portions of 25 mL). The combined organic layers were washed with ½ saturated $NaHCO_3$ aqueous solution (80 mL), brine (80 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification by flash chromatography (hexane:EtOAc, 2:1 (v:v)) delivered the title compound as a pale yellow oil (508 mg, 95%).

$R_f$ (hexane: EtOAc, 2:1 (v:v)) 0.39; $^1$H-NMR (*d*-DMSO, 200 MHz) δ 7.27 (d, 2H), 6.94 (d, 2H), 5.85 (m, 1H), 4.92-5.05 (m, 2H), 4.38-4.47 (m, 3H), 3.80 (s, 3H), 3.59-3.77 (m, 1H), 3.51-3.59 (m, 1H), 2.00-2.31 (m, 2H), 1.23-1.62 (m, 14H), 0.92 (t, 3H); $^{13}$C-NMR (DMSO, 75 MHz) (selection) δ 160.3, 140.3, 131.6, 128.7, 116.7, 116.0,

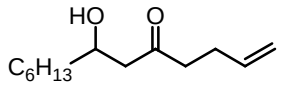
77.5, 73.1, 65.5, 43.1, 36.5, 32.3, 31.8, 28.7, 24.1, 22.7, 14.5.




**7-(4-Methoxybenzyloxy)tridec-1-en-5-one** (**5.18**)

To a 0 °C cold suspension of DMP (870 mg, 2.1 mmol, 1.4 eq.) in $CH_2Cl_2$ (9 mL) was dropwise added a solution of 7-(4-methoxybenzyloxy)tridec-1-en-5-ol (508 mg, 1.5 mmol, 1.0 eq.) in $CH_2Cl_2$ (6 mL). The resulting mixture was stirred at ice bath temperature for ½ h, allowed to reach room temperature and stirred for 1 h further. The reaction was then quenched by addition of 10% $Na_2S_2O_3$ aqueous solution (16 mL) and $NaHCO_3$ aqueous solution (45 mL) and stirred until an homogenous biphasic system was obtained (approximately 20 min.). After separation of the layers, the aqueous layer was extracted with EtOAc (2 portions of 40 mL); the combined organic layers were washed with brine (80 mL), dried ($Na_2SO_4$) and the solvent removed under vacuum to afford the title compound as a tanned yellow oil (487 mg, 96%), which was used without further purification.

$R_f$ (hexane: EtOAc, 2:1 (v:v)) 0.54; $^1$H-NMR (*d*-DMSO, 200 MHz) δ 7.22 (d, 2H), 6.90 (d, 2H), 5.80 (m, 1H), 4.93-5.01 (m, 2H), 4.40 (s, 2H), 3.82 (t, 1H), 3.78 (s, 3H), 2.75 (dd, 1H), 2.52-2.60 (m, 3H), 2.23 (q, 2H), 1.41-1.56 (m, 2H), 1.21-1.39 (m, 10H), 0.90 (t, 3H); $^{13}$C-NMR (*d*-DMSO, 75 MHz)δ 211.2, 161.0, 131.5, 132.1, 129.1, 116.3, 114.4, 73.1, 71.9, 56.6, 48.5, 43.2, 35.3, 32.0, 29.3, 29.1, 23.6, 22.6, 14.6.



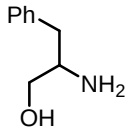

**7-Hydroxytridec-1-en-5-one *rac*-(5.5)**

**Procedure 1**: To a mixture of 7-(4-methoxybenzyloxy)tridec-1-en-5-one (**5.18**) (120 mg, 0.36 mmol, 1.0 eq.), $H_2O$ (0.17 mL) and $CH_2Cl_2$ (2.8 mL) was added DDQ (123 mg, 0.54 mmol, 1.5 eq.) in one portion. After stirring at room temperature for 2 h, $CH_2Cl_2$ (7 mL) was added and the resulting mixture was filtrated through Celite. The resulting filtrate was washed with saturated $NaHCO_3$ aqueous solution (10 mL). The organic layer was further washed with brine (2 portions of 6 mL), dried ($Na_2SO_4$) and the solvent was removed under vacuum. Purification by flash chromatography (demetallated silica gel; $CH_2Cl_2$:EtOAc, 9.5:5, (v:v)) delivered the title compound as a viscous pale yellow oil (46 mg, 60%).

**Procedure 2**: i) Preparation of LDA: To a -78 °C solution of $^{i}Pr_2NH$ (4.8 mL, 33.7 mmol, 1.28 eq.) in THF (34 mL) was dropwise added over 30 min. a solution of BuLi in hexanes (1.6 M, 20.9 mL, 33.5 mL, 1.27 eq.). After addition, the resulting faint yellow solution was allowed to slowly reach 0 °C over 15 min after which it re-cooled to -78 °C and diluted with THF (200 mL).

ii) Preparation of 7-hydroxytridec-1-en-5-one rac-(5.7): To the above LDA solution at -78 oC was dropwise added over 10 min. a solution of allylacetone (3.0 g, 30.6 mmol, 1.2 mmol) in THF (31 mL). After addition, the resulting solution was stirred for 3 min. and then a solution of heptaldehyde (3.0 g, 26.4 mmol, 1.0 eq.) in THF (29 mL) was dropwise added over 5 min. After addition, the resulting solution was stirred at -78 °C for 3 min. and then quenched at this temperature with saturated $NH_4Cl$ aqueous solution (45 mL). The reaction mixture was allowed to reach room temperature and partitioned between $H_2O$ (200 mL) and $Et_2O$ (200 mL). The aqueous layer was further extracted with $Et_2O$ (2 portions of 100 mL). The combined organic layers were washed with brine (200 mL), dried ($Na_2SO_4$) and the solvent removed under vacuum. Purification of the resulting residue by flash chromatography ($CH_2Cl_2$:EtOAc, 9.5:5, (v:v)) afforded the title compound as a viscous pale yellow oil (3.9 g, 69%).

$R_f$ ($CH_2Cl_2$: EtOAc, 9.5:0.5 (v:v)) 0.50; $^1$H-NMR (*d*-DMSO, 200 MHz) δ 5.78 (m, 1H), 4.85-5.02 (m, 2H), 4.50 (d, 1H), 3.75-3.85 (m, 1H), 2.38-2.55 (m, 4H), 2.18 (q, 2H), 1.20-1.38 (m, 10H), 0.83 (t, 3H). $^{13}$C-NMR (*d*-DMSO, 75 MHz) δ 209.6, 138.3, 115.6, 67.5, 51.0, 42.4, 38.0, 32.0., 29.4, 27.8, 25.7, 22.8, 14.7.



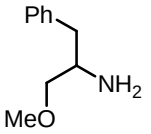

**Phenylalalinol**

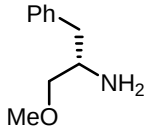
Following a literature procedure,[7.6] to an ice cold mixture of phenylalanine (20 g, 121 mmol, 1.0 eq.) and $NaBH_4$ (11 g, 292 mmol, 2.4 eq.) in THF (340 ml) was dropwise added, under an argon atmosphere and over a period of 1 h, a solution of $I_2$ (32.3 g, 127 mmol, 1.1 eq.) in THF (90 ml) (caution: strong gas evolution seen). After addition of the $I_2$ was completed and gas evolution had ceased, the mixture was gently refluxed for 18 h and the cooled to room temperature. MeOH was carefully added until the mixture became clear (approximately 25 ml of MeOH were required). After stirring for ½ h, the solvent was removed under reduced pressure affording a white paste which was dissolved by addition of a 20% aqueous NaOH solution (250 mL). The resulting solution was

[7.6] McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.

stirred for 4 h, and extracted with $CH_2Cl_2$ (3 portions of 300 mL). The combined organic layers were washed with brine (100 mL), dried ($Na_2SO_4$) and concentrated in vacuum affording a white solid. Recrystallization from hot toluene delivered the title compound as colorless crystals (13.7 g, 75%).

Mp 92-94 °C (lit.[7.6] 90-92 °C).




**1-Methoxy-3-phenylpropan-2-amine** *rac*-(**5.19**) and **(*S*)-1-Methoxy-3-phenylpropan-2-amine** (**5.19**)

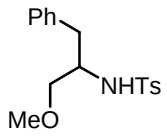
Following a literature procedure,[7.7] a solution of phenylalalinol (4 g, 26.5 mmol, 1.0 eq.) in THF (80 mL) was dropwise added to a stirred suspension of (pentane washed) NaH (1.24 g of a 55% dispersion in oil; corresponding to 0.68 g of NaH, 28.3 mmol, 1.1 eq.) in THF (30 mL) at room temperature under argon. The resulting pale yellow mixture was stirred overnight and then a solution of MeI (3.69 g, 26 mmol, 0.98 eq.) in THF (32 mL) was added dropwise over ½ h. After stirring for 3½ h, the reaction mixture was poured into ice cold brine (200 mL) and the aqueous layer was extracted with $Et_2O$ (3 portions of 150 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under vacuum affording a tan oil. Purification by reduced pressure bulb-to-bulb distillation ($T_{oven}$, 90-100 °C, 0.1-0.2 mm) delivered the title compound as a colorless oil (3.39 g, 77%).

Mp 149-152 °C (lit.[7.7] 151-152 °C); $^1$H-NMR ($CDCl_3$, 200 MHz) δ 7.05-7.23 (m, 5H), 3.12-3.35 (m, 6H), 2.72 (dd, 2H), 2.50 (dd, 2H), 1.30 (brs, 2H).

(*S*)-Methoxy-3-phenylpropan-2-amine (**5.19**) was prepared by an identical procedure starting from commercially available (*S*)-phenylalanine

$[\alpha]_D^{20}$ +19.3 (*c* 2.0, EtOH) (lit.[7.7] $[\alpha]_D^{20}$ +19.7 (*c* 2.5, EtOH)).

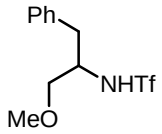
[7.7] Meyers, A. I.; Poindexter, G.; Brich, Z. B. *J. Org. Chem.* **1978**, *43*, 892.




**_N_-(1-Methoxy-3-phenylpropan-2-yl)-4-methylbenzene sulfonamide (5.20a)**

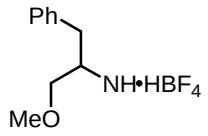
To an ice cold solution of 1-methoxy-3-phenylpropan-2-amine (**5.20**) (0.5 g, 3 mmol, 1.0 eq.) and $NEt_3$ (0.46 mL, 3.3 mmol, 1.1 eq.) in $CH_2Cl_2$ (9 mL) was dropwise added a solution of TsCl (627 mg, 3.3 mmol, 1.1 eq.) in $CH_2Cl_2$ (6 mL). After addition, the reaction mixture was allowed to reach room temperature, stirred for 20 h and then partitioned between $CH_2Cl_2$ (20 mL) and a 2 N $H_2SO_4$ aqueous solution (25 mL). The combined organic layers were washed with $H_2O$ (25 mL), brine (15 mL), dried ($MgSO_4$) and concentrated under vacuum. Purification by flash chromatography (hexane:EtOAc, 1:1 (v:v)) delivered the title compound (786 mg, 82%) as a viscous colorless oil.

$^1$H-NMR ($CHCl_3$, 200 MHz) δ 7.70 (d, 2H), 7.33 (d, 2H), 7.09-7.24 (m, 5H), 5.83 (brs, 1H), 3.72-3.79 (m, 1H), 3.60 (dd, 1H), 3.51 (dd, 1H), 3.23 (s, 3H), 2.95 (dd, 1H), 2.78 (dd, 1H), 2.56 (s, 3H).




**Trifluoro-N-(1-methoxy-3-phenylpropan-2-yl)methane sulfonamide (5.20b)**

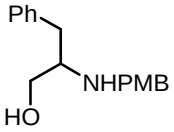
To a -78 $^oC$ cold solution of 1-methoxy-3-phenylpropan-2-amine (**5.19**) (0.4 g, 2.4 mmol, 1.0 eq.) and $N^iPr_2Et$ (0.42 mL, 2.4 mmol, 1.0 eq.) in $CH_2Cl_2$ (11 mL) was dropwise added over 10 min. a solution of $Tf_2O$ (0.4 mL, 2.4 mmol, 1.0 eq.) in $CH_2Cl_2$ (1.5 mL). After stirring at -78 $^oC$ for ½ h, an ice bath was inserted and stirring continued for ½ h further. The resulting solution was washed with 1 M HCl aqueous solution (2 portions of 8 mL); the organic layer was further washed with $H_2O$ (2 portions of 8 mL), brine (10 mL), dried ($Na_2SO_4$) and the solvent removed under vacuum. The title compound was obtained as a pale yellow oil (692 mg, 97%) which was used without further purification.




**Salt** (**5.21c**)

To an ice cold solution of 1-methoxy-3-phenylpropan-2-amine (**5.19**) (0.3 g, 1.8 mmol, 1.0 eq.) in $Et_2O$ (1.5 mL) was added $HBF_4$ (54% in $Et_2O$, 296 mg of solution, 1.8 mmol of $HBF_4$, 1.0 eq.). During addition a white precipitate formed. The obtained suspension was stirred at 0 $^oC$ for 5 min., after which period the cooling bath removed and stirring continued at room temperature for 10 min. further. The solvent was removed under reduced pressure (the

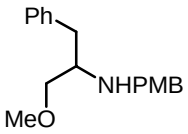
vacuum should be "broken" to an argon atmosphere) affording the title compound as white crystals (454 mg, quantitative). Note: This salt proved to be very hygroscopic and was dried in vacuum over $P_2O_5$ before being used.




**2-(4-Methoxybenzylamino)-3-phenylpropan-1-ol** (**5.24**)

Following a literature procedure,[7.8] a mixture of phenylalalinol (1.36 g, 9.0 mmol, 1.0 eq.), *p*-anisaldehyde (1.32 g, 9.7 mmol, 1.08 eq.) and 4 Å powdered MS (0.9 g) in toluene (23 mL) was heated for 2½ h at 95 °C, after which it was concentrated to dryness. The residue was taken in acetone (10 mL) and filtrated through Celite. The filtrate was concentrated under reduced pressure affording the corresponding imine as a viscous bright yellow oil. An ice cold solution of the crude imine in MeOH (23 mL) was treated with $NaBH_4$ (0.51 g, 13.5 mmol, 1.5 eq.). The resulting solution was stirred at this temperature for 45 min., quenched by the addition of acetone (4 mL), filtered through a short pad of Celite, and concentrated. The residue was dissolved in EtOAc (40 mL) and washed with $H_2O$ (20 mL). The resulting aqueous layer was further extracted with EtOAc (2 portions of 20 mL). The combined organic layers were dried ($Na_2SO_4$), the solvent was removed under vacuum to afford a yellow solid. Recrystallisation (cyclohexane:$Et_2O$, 1:1 (v:v)) delivered the title compound (2.24 g, 92 %) as a white solid.

Mp 86-88 °C (lit.[7.8] 85-86 °C); $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.15-7.37 (m, 7H), 6.79-6.86 (m, 2H), 3.78 (s, 3H), 3.71 (s, 2H), 3.64 (dd, 1H, *J* = 3.8, 10.8 Hz), 3.35 (dd, 1H, *J* = 5.2, 10.8 Hz), 2.90-2.98 (m, 1H), 2.78 (dd, 1H, *J* = 7.0, 13.2 Hz), 2.75 (dd, 1H, *J* = 7.0, 13.2 Hz), 2.02-2.48 (m, 2H).

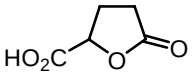



***N*-(4-Methoxybenzyl)-1-methoxy-3-phneylpropan-2-amine (5.25)**

A solution of 2-(4-methoxybenzylamino)-3-phenylpropan-1-ol (1 g, 3.69 mmol, 1.0 eq.) in THF (15 mL) was dropwise added to a stirred suspension of (pentane washed) NaH (1.24 g of a 55% dispersion in oil, corresponding to 0.68 g of NaH, 28.3 mmol, 1.1 eq.) in THF (4 mL) at room temperature under argon. The resulting pale yellow mixture was stirred for 5 h and then a solution of MeI (514 g, 3.62 mmol, 0.98 eq.) in THF (3 mL) was added dropwise. After stirring for 3½ h, the reaction mixture was poured into cold brine (30 mL) and the aqueous layer was

[7.8] Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074

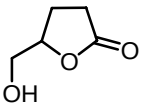
extracted with $Et_2O$ (3 portions of 50 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under vacuum affording a viscous yellow oil. Purification by flash chromatograph afforded the title compound as pale yellow oil (842 mg, 80% yield).



**5-Oxo-tetrahydrofuran-2-carboxylic acid (5.31)**

Following a literature procedure,[7.9] to a suspension of glutamic acid (29.4 g, 200 mmol, 1.0 eq.) in $H_2O$ (300 mL) at 10 $^oC$ are added simultaneously and at the same rate, over a 2 h period, a solution of $NaNO_2$ (16.8 g, 243 mmol, 1.2 eq.) in $H_2O$ (240 mL) and an aqueous 1 N $H_2SO_4$ solution (240 mL). The mixture was then allowed to reach room temperature and stirred overnight. The obtained solution was concentrated under vacuum ($T_{H2O\ bath} < 45\ ^oC$). The syrup residue produced was extracted with hot EtOAc (4 portions of 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum affording the tile compound (15.8 g, 60% yield) as a pale yellow oil that was used directly.

$^1$H-NMR ($CHCl_3$, 200 MHz) δ 5.00-5.10 (m, 1H), 2.51-2.65 (m, 3H), 2.20-2.40 (m, 2H); $^{13}$C ($CHCl_3$, 75 MHz) δ 181.0, 174.0, 77.1, 27.4, 25.5. LRMS (EI) *m/z* = 131 [$M^+$].

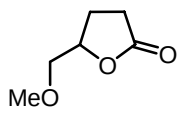


**4-Hydroxymethyl-4-butyrolactone**

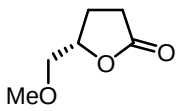
Following a literature procedure,[7.9] to chilled solution of the crude 5-oxo-tetrahydrofuran-2-carboxylic acid (5.33) (15 g, 115 mmol, 1.0 eq.) in THF (115 mL) was dropwise added, over 2 h, a solution of $BH_3{\cdot}SMe_2$ (2 M in THF, 72 mL, 143 mmol, 1.2 eq.) (caution: strong gas evolution). After stirring at room temperature for 3 h, the solution was cooled to ice bath temperature, MeOH (90 mL) was carefully added and the resulting solution was concentrated under reduced pressure. The yellow oil obtained was re-dissolved in MeOH (150 mL), re-concentrated under vacuum and the oil obtained was purified by reduced pressure bulb-to-bulb distillation ($T_{oven}$ 120-130 $^oC$, 0.4 mm; lit.[7.9] 122-130 $^oC$, 0.6 mm). The title compound was delivered as a colorless oil (9.5 g, 71%).

$^1$H NMR ($CDCl_3$, 200 MHz) δ 2.2-2.8 (m, 4H), 3.60-4.10 (m, 3H), 4.6 (m, 1H). LRMS (EI) *m/z* = 117 [$M^+$].

[7.9] Larcheveque, M.; Lalande, J. *Tetrahedron* **1984**, *40*, 1061.



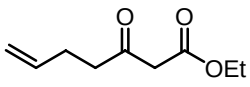

**γ-(Methoxymethyl)- γ-butyrolactone *rac*-(5.30)** and
**(*S*)-γ-(Methoxymethyl)- γ-butyrolactone (5.30)**




Following a literature procedure,[7.10] a solution of 4-hydroxymethyl-4-butyrolactone (2.0 mL, 21.3 mmol, 1.0 eq.) in THF (8 mL) was dropwise added over approximately 5 min. to a stirred suspension of (pentane washed) NaH (1.1 g of a 60% NaH dispersion in oil; corresponding to 660 mg of NaH, 27.5 mmol, 1.2 eq.) in THF (39 mL) at 0 °C under argon. After addition, the resulting gelatinous mixture was allowed to reach room temperature and stirred for 5 h (note: occasional external stirring was necessary). The mixture was then re-cooled to 0 °C and a solution of MeI (9.1 g, 63.9 mmol, 3 eq.) in THF (8 mL) was added dropwise over 5 min.. The pale yellow mixture obtained was stirred overnight at room temperature. The reaction was quenched by addition of ½ saturated aqueous $NH_4Cl$ (50 mL) at 0 °C and extracted with $CH_2Cl_2$ (100 mL). The aqueous layers was further extracted with $CH_3Cl$ (100 mL). The combined organic layers were washed with brine (30 mL), dried ($Na_2SO_4$) and concentrated under vacuum to afford a pale yellow oil (2.2 g, 80%) that was used without further purification.

$^1$H NMR ($CDCl_3$, 200 MHz) 1.82-2.70 (m, 4H), 3.42 (s, 3H), 3.55 (d, 2H), 4.40-4.75 (m, 1H). LRMS (EI) *m/z* = 130 [$M^+$].

(*S*)-γ-(Methoxymethyl)-γ-butyrolactone (**5.32**) was prepared by an identical procedure starting from the commercially available (*S*)-hydroxymethyl-γ-butyrolactone. $[\alpha]_D^{20}$ +27.7 (*c* 0.80, $CHCl_3$) (lit.[7.10] $[\alpha]_D^{20}$ +27.9 (*c* 0.86, $CHCl_3$)).



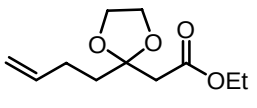

**Ethyl 3-oxohept-6-enoate**

Following a literature procedure,[7.11] ethylacetoacetate (6.0 g, 46.1 mmol, 1.0 eq.) was added dropwise over 15 min. to a stirred suspension of (pentane washed) NaH (2.2 g of a 60% NaH dispersion in oil; corresponding to 1.22 g of NaH, 50.7 mmol, 1.1 eq.) in THF (115 mL) at 0 °C. After stirring at this temperature for 15 min., a solution of BuLi (1.6 M in hexanes, 30.5 mL, 1.05 eq.) was added dropwise over 25 min.. The resulting orange solution was stirred for further 15 min. at 0 °C, after which a solution of freshly distilled allyl bromide (4.4 mL, 50.7

[7.10] Nemoto, H.; Nagai, M.; Fukumoto, K. *J. Org. Chem.* **1985**, *50*, 2764.
[7.11] Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

mmol, 1.1 eq.) in THF (9 mL) was added in a dropwise manner over 15 min. at this temperature. The solution was allowed to slowly warm to room temperature, stirred for 15 min., recooled to 0 °C and carefully quenched with an aqueous solution of HCl (9 mL of concentrated HCl in 23 mL of $H_2O$). The reaction mixture was then partitioned between $H_2O$ (20 mL) and $Et_2O$ (90 mL) and the aqueous layer was extracted with $Et_2O$ (2 portions of 30 mL). The combined organic layers were washed with $H_2O$ until neutral (typically 5-6 washes of 120 mL $H_2O$ were required). The organic layer was dried ($MgSO_4$) and the solvents were removed under vacuum. Purification by distillation under reduced pressure (44-46 °C, 0.2 mm; lit.[6.11] 99-100 oC, 15 mm) afforded the title compound as a colorless oil (7.1 g, 91%).

$^1$H-NMR ($CDCl_3$, 200 MHz) δ 5.7-5.8 (m, 1H), 4.8-5.1 (m, 2H), 4.1 (q, 2H), 3.4 (s, 2H), 2.6 (t, 2H), 2.2-2.3 (m, 2H), 1.2 (t, 3H).

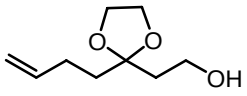



**Ethyl 3,3-(ethylenedioxy)-6-heptenoate** (**5.32**)

Following the procedure reported by Baldwin and co-workers,[7.12] a mixture of ethyl 3-oxohept-6-enoate (11.8 g, 69.3 mmol, 1.0 eq.), ethylene glycol (12.9 g, 208 mmol, 3 eq.) and a few crystals of $TSOH \cdot H_2O$ in benzene (500 mL) was refluxed over 15 h with mechanical removal of $H_2O$ (Dean-Stark separator). During this period the collecting arm in the Dean Stark separator was emptied 4 times. The resulting mixture was cooled to room temperature, washed with saturated $NaHCO_3$ aqueous solution (3 portions of 250 mL), brine (150 mL), dried ($Na_2SO_4$) and concentrated under reduced pressure to afford a tan oil. Purification by bulb-to-bulb distillation at reduced pressure ($T_{oven}$ 130-135 °C, 0.1 mm) yielded the title compound as a faint yellow oil (11.4 g, 77%).

Rf (hexane:EtOAc, 3:2 (v:v)) 0.44; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 5.7-5.9 (m, 1H), 4.9-5.1 (2H, m), 4.2 (t, 2H), 3.9-4.0 (m, 4H), 2.6 (s, 2H), 2.1-2.3 (m, 2H), 1.9-2.0 (m, 2H), 1.3 (t, 3H).

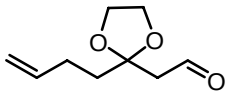
[7.12] Baldwin, S. W.; Wilson, J. D.; Aubé, J. *J. Org. Chem.* **1985**, *50*, 4432.



**3,3-(Ethylenedioxy)-6-hepten-1-ol**

Following a literature procedure,[7.12] to a stirred mixture of $LiAH_4$ (2.18 g, 57.2 mmol, 1.07 eq.) in $Et_2O$ (125 mL) was dropwise added over 20 min. a solution of ethyl 3,3-(ethylenedioxy)-6-heptenoate (5.32) (11.4 g, 53.3 mmol, 1.0 eq.) in $Et_2O$ (10 mL) at 0 °C. After stirring for 3½ h at room temperature, the reaction was recooled to 0 °C and carefully quenched by sequential addition of $H_2O$ (2.4 mL), 10% NaOH aqueous solution (3.2 mL) and $H_2O$ (6.5 mL). The mixture obtained was stirred overnight at room temperature. After filtration, the salts were filtered and washed thoroughly with $Et_2O$ (4 portions of 100 mL) and the combined ethereal solutions concentrated. The residue was taken in $CH_2Cl_2$ (200 mL), dried ($Na_2SO_4$) and concentrated to yield the title alcohol as a pale yellow oil (8.53 g, 93%) which was used directly in the next step.

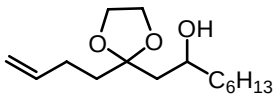
Rf (hexane:EtOAc, 3:2 (v:v)) 0.18; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 5.7-5.9 (m, 1H), 4.8-5.1 (m, 2H), 3.9-4.0 (m, 4H), 3.7 (t, 2H), 2.7 (brs, 1H), 2.0-2.2 (m, 2H), 1.9 (t, 2H), 1.6 (m, 2H).



**3,3-(Ethylenedioxy)-6-heptenal** (**5.33**)

To a 0 °C cold suspension of DMP (13.3 g, 31.4 mmol, 1.2 eq.) in $CH_2Cl_2$ (125 mL) was dropwise added a solution of 3,3-(ethylenedioxy)-6-hepten-1-o (4.5 g, 26.1 mmol, 1.0 eq.) in $CH_2Cl_2$ (104 mL). The resulting mixture was stirred at ice bath temperature for ½ h, allowed to reach room temperature and stirred for 1 h further. The reaction was then quenched by addition of 10% $Na_2S_2O_3$ aqueous solution (225 mL) and $NaHCO_3$ aqueous solution (540 mL) and stirred until an homogenous biphasic system was obtained (approximately 20 min.). After separation of the layers, the aqueous layer was extracted with EtOAc (2 portions of 150 mL); the combined organic layers were washed with brine (150 mL), dried ($Na_2SO_4$) and the solvent removed under vacuum to afford the known aldehyde as a pale yellow oil (4.4 g, quantitative), which was used without further purification.

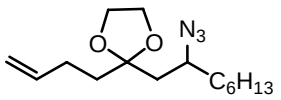
Rf (hexane:EtOAc, 3:2, (v:v)) 0.38; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 5.7-5.9 (m, 1H), 4.8-5.0 (m, 2H), 3.9 (s, 4H), 2.8 (s, 2H), 2.0-2.2 (m, 2H), 1.7-1.8 (m, 2H).



**1-(2-(But-3-enyl)-1,3-dioxalan-2-yl)octan-2-ol** (**5.34**)

To a ice cold solution of hexylmagnesium bromide (2 M in $Et_2O$, 15.5 mmol, 1.15 eq.) in $Et_2O$ (12 mL) was dropwise added over 20 min. a solution of 3,3-(ethylenedioxy)-6-heptenal (**5.33**) (2.30 g, 13.5 mmol, 1.0 eq.) in $Et_2O$ (13 mL). The resulting solution was allowed to reach room temperature, stirred for 1 h, recooled to 0 $^oC$ and quenched with saturated $NH_4Cl$ aqueous solution (10 mL). After separation of the layers, the aqueous layer was extracted with $Et_2O$ (20 ml). The combined organic layers were washed with brine (25 mL), dried ($Na_2SO_4$), the solvent removed under vacuum affording a pale yellow oil. Purification by bulb-to-bulb distillation at reduced pressure ($T_{oven}$ 120-130 $^oC$, 0.05 mm) yielded the title compound as a faint yellow oil (2.6 g, 75%).

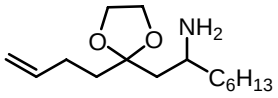
$R_f$ (hexane: EtOAc, 3:2 (v:v)) 0.47; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.75 (ddt, *J* = 17.0, 10.2, 6.5 Hz, 1H), 4.95 (d´q´, *J* = 1.6, 17.0 Hz, 1H), 4.85 (d´q´, *J* = 1.6, 10.2 Hz, 1H), 3.88-3.96 (m, 4 H), 3.75-3.83 (m, 1H), 3.47 (brs, 1H), 2.01-2.10 (m, 2H), 1.62-1.75 (m, 4H), 1.16-1.28 (m, 10H), 0.79-0.83 (m, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 138.3, 114.7, 112.1, 68.1, 65.1, 64.9, 43.1, 37.7, 36.7, 32.1, 29.6, 28.3, 25.7, 22.8, 14.3.



**2-(2-Azidooctyl)-2-(but-3-enyl)-1,3-dioxalane**

To a 0 $^oC$ cold solution of 1-(2-(but-3-enyl)-1,3-dioxalan-2-yl)octan-2-ol (**5.34**) (1.30 g, 5.1 mmol, 1.0 eq.) and $PPh_3$ (2.71 g, 10.1 mmol, 2 eq.) in THF (39 mL) was dropwise added over 20 min. DIAD (2.10 g, 10.1 mmol, 2 eq.). The resulting beige suspension was stirred for 5 min., after which DPPA (1.54 g, 5.6 mmol, 1.1 eq.) was dropwise added over 15 min.. After stirring at 0 $^oC$ for 36 h, the suspension was filtered and the solid residue rinsed with cold THF (2 portions of 15 mL). The combined filtrates were concentrated under vacuum and the obtained residue was purified by flash chromatography (hexane:EtOAc, 3:2 (v:v)). The title compound was obtained as a pale yellow oil (1.33 g, 93%).

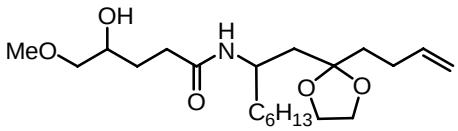
$R_f$ (hexane: EtOAc, 3:2 (v:v)) 0.65; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.75 (ddt, *J* = 6.5, 10.2, 16.8 Hz, 1H), 4.96 (d´q´, *J* = 1.6, 16.8 Hz, 1H), 4.88 (d´q´, *J* = 1.6, 10.2 Hz, 1H), 3.87-3.94 (m, 4 H), 3.30-3.80 (m, 1H), 2.02-2.11 (m, 2H), 1.19-1.75 (m, 14H), 0.77-0.86 (m, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 138.4, 114.7, 110.4, 65.2, 65.1, 58.9, 41.5, 37.0, 36.0, 31.9, 29.2, 28.3, 26.2, 14.3.



**1-(2-(But-3-enyl)-1,3-dioxolan-2-yl)octan-2-amine** *rac*-(**5.29**).

To a 0 °C cold suspension of $LiAH_4$ (472 mg, 12.4 mmol, 2.8 eq.) in $Et_2O$ (32 mL) was dropwise added over 20 min. a solution of 2-(2-azidooctyl)-2-(but-3-enyl)-1,3-dioxalane (1.25 g, 4.44 mmol, 1.0 eq.) in $Et_2O$ (34 mL). The resulting mixture was stirred for 1½h at 0 °C and for 3 h further at room temperature, after which it was recooled to 0 °C and carefully quenched by sequential dropwise addition of $H_2O$ (0.5 mL), 10% NaOH aqueous solution (0.5 mL) and $H_2O$ (1 mL). After stirring for 5 min. the mixture was filtered, the salts washed thoroughly with EtOAc (2 portions of 15 mL). The combined organic layers were washed with brine (40 mL), dried ($Na_2SO_4$) and concentrated under vacuum to afford the title compound as a pale yellow oil (1.04 g, 92%) which was used without further purification.

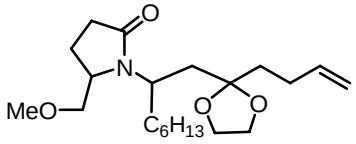
$R_f$ (hexane: EtOAc, 3:2 (v:v)) 0.0; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.78 (ddt, *J* = 6.5, 10.1, 17.0 Hz, 1H), 4.96 (d´q´, *J* = 1.4, 17.0 Hz, 1H), 4.84 (d´q´, *J* = 1.4, 10.1 Hz, 1H), 3.82-3.94 (m, 4 H), 2.83-2.95 (m, 1H), 2.21-2.39 (brs, 2H), 2.00-2.13 (m, 2H), 1.50-1.78 (m, 4H), 1.17-1.38 (m, 10H), 0.77-0.86 (m, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 138.6, 114.6, 111.8, 65.1, 64.8, 47.6, 44.1, 39.0, 36.8, 32.0, 29.6, 28.4, 26.2, 22.8, 14.3; LRMS (EI) *m/z* = 170 [$M^+$-$C_6H_{13}$].



***N*-(1-(2-(but-3-enyl)-1,3-dioxalan-2-yl)octan-2-yl)-4-hydroxy-5-methoxypentanamide** (**5.35**)

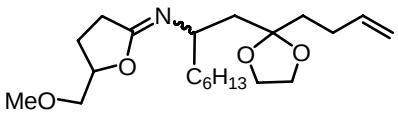
To a ice cold solution of *γ*-(methoxymethyl)-*γ*-butyrolactone *rac*-(**5.30**) (2.0 g, 15.3 mmol, 1.0 eq.) in toluene (40 mL) was dropwise added over 20 min. a solution of $AlMe_3$ (2 M in hexanes, 9.2 mL, 1.2 eq.). After being stirred for 15 min. at room temperature, a solution of 1-(2-(but-3-enyl)-1,3-dioxolan-2-yl)octan-2-amine *rac*-(**5.29**) (4.11 g, 16.1 mmol, 1.05 eq.) was dropwise added over 15 min. at 0 °C. The resulting solution was stirred at room temperature for 15 min., refluxed for 1½ h, recooled to 0 °C, very carefully quenched with saturated $NH_4Cl$ aqueous solution (25 mL) and extracted with EtOAc (150 mL). The aqueous layer was further extracted with EtOAc (100 mL). The combined organic layers were washed with brine (100 mL), dried ($Na_2SO_4$) and the solvents removed under vacuum to afford the title compound as a pale yellow oil (5.52 g, 94%).

$R_f$ ($CHCl_3$: MeOH, 9:1 (v:v)) 0.45; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.84 (brs, 1H), 5.74 (ddt, *J* = 6.6, 10.0, 16.8 Hz, 1H), 4.95 ('d', *J* = 16.9 Hz, 1H), 4.87 ('d', *J* = 10.0 Hz, 1H), 3.65-3.95 (m, 6H), 3.20-3.37 (m, 5H), 2.27 (t, *J* = 7.0 Hz, 2H), 2.00-2-09 (m, 2H), 1.75-1.84 (m, 2H), 1.56-1.68 (m, 4H), 1.39-1.47 (m, 2H), 1.17-1.25 (m, 8H), 0.78-0.82 (m, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 171.4, 137.1, 113.4, 109.9, 71.3, 68.8, 68.7, 58.0, 45.2, 39.7, 35.7, 35.0, 32.5, 32.1, 30.0, 29.8, 28.2, 24.5, 21.7, 13.0; LRMS (EI) *m/z* = 385 [$M^+$].




**5.38**

and




**5.39**

**1-(1-(2-But-3-enyl)-1,3-dioxolan-2-yl)octan-2-yl)-5-(methoxymethyl)pyrrolidin-2-one** (**5.36**) and **1-(2-(but-3-enyl)-1,3-dioxolan-2-yl)-*N*-(5-(methoxymethy)-dihydrofuran-2(3H)-ylidene)octan-2-amine** (**5.37**)

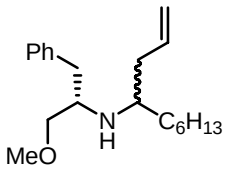
i) Preparation of 5-(1-(2-(but-3-enyl)-1,3-dioxolan-2-yl)octan-2-ylamino)-1-methoxy-5-oxopentan-2-yl methanesulfonate: To an ice cold solution of *N*-(1-(2-(but-3-enyl)-1,3-dioxalan-2-yl)octan-2-yl)-4-hydroxy-5-methoxypentanamide (**5.37**) (5.58 g, 14.4 mmol, 1.0 eq.) and $NEt_3$ (3 mL, 21.7 mmol, 1.5 eq.) in $CH_2Cl_2$ (72 mL) was dropwise added MsCl (1.35 mL, 17.5 mmol, 1.2 eq.). The reaction mixture was stirred at 0 $^oC$ for 1 h after which period it was washed with an 0.5 M HCl aqueous solution (50 mL), ½ saturated $NaHCO_3$ aqueous solution (200 mL), $H_2O$ (60 mL), brine (60 mL) and dried ($Na_2SO_4$). Removal of the solvent under vacuum delivered the title compound as a pale yellow oil (6.4 g, 95%) which was used directly.

ii) Preparation of 1-(1-(2-but-3-enyl)-1,3-dioxolan-2-yl)octan-2-yl)-5-(methoxymethyl)pyrrolidin-2-one (**5.38**) and 1-(2-(but-3-enyl)-1,3-dioxolan-2-yl)-*N*-(5-(methoxymethy)-dihydrofuran-2(3H)-ylidene)octan-2-amine (**5.39**): A mixture of 5-(1-(2-(but-3-enyl)-1,3-dioxolan-2-yl)octan-2-ylamino)-1-methoxy-5-oxopentan-2-yl methanesulfonate (6.3 g, 13.7 mmol, 1.0 eq.) and $^t$BuOK (3.25 g, 28.9 mmol, 2 eq.) in toluene (110 mL) was stirred at room temperature for 1½ h, after which it was partitioned between a saturated $KHSO_4$ aqueous solution (340 mL) and EtOAc (400 mL). The aqueous layer was further extracted with EtOAc (2 portions of 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (2 portions of 200 mL), brine (100 mL), dried ($Na_2SO_4$) and the solvents removed

under vacuum. The residue obtained was purified by flash chromatography (hexane:EtOAc 3:2, (v:v)) to afford 1-(1-(2-but-3-enyl)-1,3-dioxolan-2-yl)octan-2-yl)-5-(methoxymethyl)pyrrolidin-2-one (**5.36**) (2.59 g, 51%) and 1-(2-(but-3-enyl)-1,3-dioxolan-2-yl)-*N*-(5-(methoxymethy)-dihydrofuran-2(3H)-ylidene)octan-2-amine (**5.37**) (654 mg, 13%).

For 1-(1-(2-but-3-enyl)-1,3-dioxolan-2-yl)octan-2-yl)-5-(methoxymethyl)pyrrolidin-2-one (**5.36**):
$R_f$ ($CHCl_3$: MeOH, 9:1 (v:v)) 0.88; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.68-5.83 (m, 1H), 4.95 ('d', *J* = 17.2 Hz, 1H), 4.86 ('d', *J* = 10.2 Hz, 1H), 3.52-4.07 (m, 6H), 3.25-3.38 (m, 5H), 1.62-2.45 (m, 12H), 1.14-1.20 (m, 8H), 0.78-0.82 (m, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) (selected) δ 176.2, 138.3, 114.4, 111.5, 75.3, 65.0, 59.1, 58.0, 51.5, 49.3, 39.8, 38.0, 37.7, 36.6, 33.4, 32.0, 29.3, 28.3, 27.1, 22.8, 14.3; IR (neat): 1684 $cm^{-1}$; LRMS (EI) *m/z* = 367 [$M^+$].

For 1-(2-(but-3-enyl)-1,3-dioxolan-2-yl)-*N*-(5-(methoxymethy)-dihydrofuran-2(3H)-ylidene)octan-2-amine (**5.37**):
$R_f$ ($CHCl_3$: MeOH, 9:1 (v:v)) 0.40; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.68-5.84 (m, 1H), 4.82-5.00 (m, 2H), 4.40-4.49 (m, 1H), 3.72-3.91 (m, 5H), 3.26-3.47 (m, 5H), 2.42-2.2.56 (m, 2H), 1.57-2.19 (m, 10H), 1.09-1.35 (m, 8H), 0.77-0.82 (m, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) (selected) δ 170.3, 139.2, 115.3, 111.8, 80.3, 74.8, 64.8, 59.6, 52.5, 41.8, 36.736.4, 33.4, 32.2, 29.7, 29.5, 29.1, 28.3, 26.5, 22.9, 14.3; IR (neat): 1725 $cm^{-1}$; LRMS (EI) *m/z* = 367 [$M^+$].




**(*S*)-*N*-(1-methoxy-3-phenylpropan-2-yl)dec-1-en-4-amine** (**5.47**)

i) Preparation of aldimine (*S*)-(**5.46a**): A mixture of (S)-1-methoxy-3-phenylpropan-2-amine (**5.19**) (150 mg, 0.91 mmol, 1.0 eq.), heptaldehyde (114 mg, 1.0 mmol, 1.1 eq.) and $Na_2SO_4$ (258 mg, 1.8 mmol, 2 eq.) in $CH_2Cl_2$ (2 mL) was stirred at room temperature for 2½h. After filtration, the filtrate was concentrated at reduced pressure affording the crude aldimine (**5.46a**) which was used directly in the subsequent reaction.

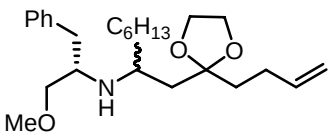
ii.2) Preparation of (*S*)-*N*-(1-methoxy-3-phenylpropan-2-yl)dec-1-en-4-amine (**5.47**) (*via* reaction with allylMgBr): A solution of allylmagnesiumbromide (0.7 M in Et2O, 1.3 mL, 3 eq.) was dropwise added to a -78 °C cold solution of crude aldimine (**5.46a**) (78 mg, 0.3 mmol, 1.0 eq.) in THF (1.8 mL).The resulting mixture was stirred at the

same temperature for 3 h after, allowed to slowly reach room temperature and quenched by careful addition of $H_2O$ (2 mL). The aqueous layer was extracted with EtOAc (2 portions of 5 mL). The combined organic layers were washed with brine (3 mL), dried (Na2SO4) and the solvents removed under vacuum affording a pale yellow oil. Purification by flash chromatography (hexane:EtOAc 4:1, (v:v)) delivered the title compound as a pale yellow oil (40 mg, 44%).

ii.2) Preparation of (*S*)-*N*-(1-methoxy-3-phenylpropan-2-yl)dec-1-en-4-amine (**5.47**) (*via* reaction with "allylCeCl$_2$"): A suspension of (freshly prepared) $CeCl_3$ (160 mg, 0.65 mmol, 2.0 eq.) in THF (3.5 mL) was stirred for 15 h at room temperature under argon. After this ageing period, the suspension was cooled to -50 $^oC$ and a solution of allylmagnesiumbromide (0.7 M in $Et_2O$, 0.9 mL, 2.0 eq.) was dropwise added. The resulting mixture was stirred at the same temperature for ½ h, after which a solution of (freshly prepared) crude aldimine (**5.46a**) (83 mg, 0.32 mmol, 1.0 eq.) in THF (1 mL) was dropwise added. Stirring continued for 2 h at the same temperature, the reaction was then slowly warmed to room temperature, stirred for an additional 3 h and poured into brine (10 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (2 portions of 5 mL); the combined organic layers were washed with brine (10 mL), dried ($Na_2SO_4$) and concentrated in vacuum to afford a tan residue. Purification by flash chromatography (hexane:EtOAc 4:1, (v:v)) delivered the title compound as a pale yellow oil (51 mg, 52%).

ii.3) Preparation of (*S*)-*N*-(1-methoxy-3-phenylpropan-2-yl)dec-1-en-4-amine (**5.47**) (*via* reaction with "allylCuBF$_3$"): To a suspension of CuI (366 mg, 1.92 mmol, 5.0 eq.) in THF (3 mL) at – 55 $^oC$ was dropwise added over 5 min. a solution of allylmagnesiumbromide (0.7 M in $Et_2O$, 2.7 mL, 2.0 eq.). The resulting mixture was cooled to -78 oC, stirred for 15 min. and $BF_3.OEt_2$ (0.24 ml, 1.92 mmol, 5.0 eq.) was dropwise added. After stirring 5 min. at the same temperature, a solution of crude aldimine (**5.46a**) (100 mg, 0.38 mmol, 1.0 eq.) in THF (1.5 mL) was dropwise added. Stirring continued for 3 h at the same temperature, the reaction was then slowly warmed to room temperature, stirred for an additional 3 h and poured into saturated $NaHCO_3$ aqueous solution (10 mL) and EtOAc (20 mL). The aqueous layer was further extracted with EtOAc (2 portions of 5 mL). The combined organic layers were washed with $H_2O$ (10 mL), brine (10 mL), dried ($Na_2SO_4$) and concentrated under vacuum to afford a tan oil. Purification by flash chromatography (hexane:EtOAc 4:1, (v:v)) delivered the title compound as a pale yellow oil (64 mg, 56%).

$R_f$ (hexane: EtOAc, 1:1 (v:v)) 0.63; $^1$H-NMR ($CDCl_3$, 300 MHz) (the two diastereomers are reported together) δ 7.15-7.29 (m, 5H), (5.78 (ddt, *J* = 7.1, 10.2, 17.2 Hz), 5.60 (ddt, J = 7.3, 10.7, 17.4 Hz), 1H), (5.00-5.08 (m), 4.84-4.94 (m), 1H), (3.31 (s), 3.30 (s), 3H), 3.21 (dd, *J* = 1.7, 5.0 Hz, 2H), 2.96 (m, 1H), 2.70 (d, *J* = 6.8 Hz, 2H), 2.60 (m, 1H), (2.13 (´t´, *J* = 6.9 Hz), 2.02 (m), 2H), 1.08-1.38 (m, 10H), 0.86 (t, *J* = 6.7 Hz, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) (selection) δ 139.2, 137.9, 129.2, 128.2, 127.0, 116.3, 80.1, 59.7, 53.1, 52.6, 41.6, 39.7, ;36.0, 31.9, 29.7, 23.5, 22.9, 13.8; LRMS (EI) *m/z* = 258 [$M^+$-$C_2H_5O$].



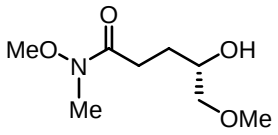

**(*S*)-1-(2-(But-3-neyl)-1,3-dioxalan-2-yl)-*N*-(1-methoxy-3-phneylpropan-2-yl)octan-2-amine** (**5.51**)

i) Preparation of aldimine (*S*)-(**5.4bb**): A mixture of (1-(*S*)-methoxy-3-phenylpropan-2-amine (**5.19**) (500 mg, 3.0 mmol, 1.0 eq.), 3,3-(ethylenedioxy)-6-heptenal (**5.33**) (542 mg, 3.2 mmol, 1.05 eq.) and $Na_2SO_4$ (860 mg, 7.1 mmol, 2.3 eq.) in $CH_2Cl_2$ (3.5 mL) was stirred at room temperature for 3 h. After filtration, the filtrate was concentrated at reduced pressure affording the crude aldimine (*S*)-(**5.4bb**) which was used directly in the subsequent reaction.

ii) Preparation of (*S*)-1-(2-(but-3-neyl)-1,3-dioxalan-2-yl)-*N*-(1-methoxy-3-phneylpropan-2-yl)octan-2-amine (**5.51**): A suspension of (freshly prepared) $CeCl_3$ (781 mg, 3.17 mmol, 5.0 eq.) in THF (16 mL) was stirred for 15 h at room temperature under argon. After this ageing period, the suspension was cooled to -50 $^o$C and a solution of hexylmagnesiumbromide (2 M in $Et_2O$, 1.58 mL, 5.0 eq.) was dropwise added. The resulting mixture was stirred at the same temperature for ½ h, after which a solution of (freshly prepared) crude aldimine (**5.46b**) (200 mg, 0.63 mmol, 1.0 eq.) in THF (2 mL) was dropwise added. Stirring continued for 2 h at the same temperature, the reaction was then slowly warmed to room temperature, stirred for an additional 10 h and poured into brine (20 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (2 portions of 15 mL); the combined organic layers were washed with brine (15 mL), dried ($Na_2SO_4$) and concentrated in vacuum. Purification of the residue obtained by flash chromatography (hexane:EtOAc 1:1, (v:v)) delivered the title compound as a pale yellow oil (153 mg, 60%).

$R_f$ (hexane: EtOAc, 1:1 (v:v)) 0.15; $^1$H-NMR ($CDCl_3$, 300 MHz) (the two diastereomers are reported together) δ 7.09-7.23 (m, 5H), 5.73 (ddt, *J* = 6.5, 10.1, 16.7 Hz, 1H), 4.93 (dq, *J* = 1.7, 16.7 Hz, 1H), 4.86 (´d´, *J* = 10.1 Hz, 1H), 3.81-3.84 (m, 4H), 3.24 (s, 3H), 3.15-3.17 (brd, 2H), 2.60-2.88 (m, 4H), 1.91-2.1 (m, 2H), 1.50-1.75

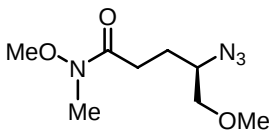
(m, 4H), 1.1-1.41 (m, 10H), 0.78-0.83 (m, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) (selection) δ 140.3, 138.7, 129.6, 128.5, 126.2, 114.6, 111.6, 75.3, 65.0, 64.7, 59.1, 56.8, 51.7, 42.0, 38.3, 36.7, 36.1, 32.1, 29.8, 28.4, 25.6, 22.9, 14.3; LRMS (EI) *m/z* = 358 [$M^+$-$C_2H_5O$].




**(*S*)-4-Hydroxy-*N*,5-dimethoxy-*N*-methylpentanamide (5.55)**

To an ice cold suspension of HCl·NH(OMe)Me (4.10 g, 42.1 mmol, 4.0 eq.) in $CH_2Cl_2$ (85 mL) was dropwise added over 15 min. a solution of $AlMe_2Cl$ (1 M in hexane, 42.2 mL, 4.0 eq.) during which gas evolution was observed. The mixture was slowly warmed to room temperature and stirred at for 1½ h further. A solution of (*S*)-γ-(methoxymethyl)-γ-butyrolactone (**5.30**) (1.37 g, 10.5 mmol, 1.0 eq.) in $CH_2Cl_2$ (85 mL) was added dropwise over ½ h and the mixture was stirred overnight, cooled to 0 °C, carefully quenched with a saturated $NH_4Cl$ aqueous solution (150 mL). The salts were filtered (a short pad of Celite was used) and washed with $CH2Cl_2$ (2 portions of 20 mL). The filtrates were combined, the layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (2 portions of 30 mL). The combined organic layers were washed with brine (150 mL), dried ($Na_2SO_4$) and the solvent removed in vacuum. The residue obtained was filtered through a short column of silica gel ($CHCl_3$:MeOH, 9:1, (v:v)) affording the title compound as a pale yellow oil (1.81 g, 90%). The title compound was obtained as a colorless oil (1.42 g, 82%). Note: High vacuum should be avoided

$R_f$ ($CHCl_3$: MeOH, 9:1 (v:v)) 0.67; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 3.75-3.82 (m, 1H), 3.68 (s, 3H), 3.26-3.40 (m, 5H), 3.17 (s, 3H), 2.60 (′t′, *J* = 7.4 Hz, 2H), 1.64-1.89 (m, 2H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 174.5, 78.6, 70.0, 61.4, 59.2, 32.5, 28.4, 28.1. LRMS (EI) *m/z* = 192 $[M+H]^+$; $[\alpha]_D^{25}$ +9.3 (*c* 1.9, $CHCl_3$).

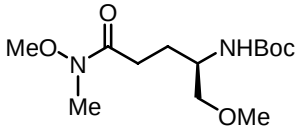



**(*R*)-4-Azido-*N*,5-dimethoxy-*N*-methylpentanamide**

To an ice cold solution of (*S*)-4-hydroxy-*N*,5-dimethoxy-N-methylpentanamide (**5.55**) (1.53 g, 8.0 mmol, 1.0 eq.) and PPh3 (3.77 g, 14.4 mmol, 1.8 eq.) in THF (61 mL) was dropwise added over 15 min. a solution of DIAD (2.91 g, 14.4 mmol, 1.8 eq.) in THF (1 mL). The resulting mixture was stirred for 20 min, after which a solution of DPPA (2.42 g, 8.8 mmol, 1.1 eq.) in THF (2 mL) was dropwise added. After stirring for 6½ h at room temperature, most of the solvent was removed under vacuum and the residue was purified by flash

chromatography (hexane:EtOAc 3:2, (v:v)). The title compound was obtained as a colorless oil (1.42 g, 82%). Note: High vacuum should be avoided.

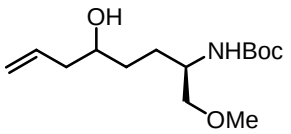
$R_f$ (hexane: EtOAc, 3:2 (v:v)) 0.15; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 3.64 (s, 3H), 3.35-3.57 (m, 3H), 3.33 (s, 3H), 3.12 (s, 3H), 2.50 (´t´, $J$ = 8.0 Hz, 2H), 1.57-1.88 (m, 2H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 173.6, 75.6, 61.5, 61.2, 59.3, 32.5, 28.4, 26.0; $[\alpha]_D^{25}$ +14.5 (*c* 2.1, $CHCl_3$).




**(*R*)-tert-Butyl 1-methoxy-5-(methoxy(methyl)amino)-5-oxopenta-2-ylcarbamate** (**5.56**)

A vigorously stirred suspension of (*R*)-4-azido-*N*,5-dimethoxy-*N*-methylpentanamide (1.16g, 5.37 mmol, 1.0 eq.), $Boc_2O$ (1.41 g, 6.45 mmol, 1.2 eq.), and 5% Pd on carbon (320 mg) in EtOAc (12 mL) was subjected to a atmosphere of $H_2$ (balloon) overnight at room temperature and filtrated through a Celite pad, which was rinsed with EtOAc (2 portions of 5 mL). The combined filtrates were evaporated at reduced pressure and the residue was purified by flash chromatography ($CHCl_3$:MeOH 9:1, (v:v)) affording the title compound as a pale yellow oil (1.45 g, 93%). Note: High vacuum should be avoided.

$R_f$ ($CHCl_3$:MeOH, 9:1 (v:v)) 0.48; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 4.79 (brs, 1H), 3.65-3.78 (m, 1H) (partial overlap with s at 3.67 ppm), 367 (s, 3H) (partial overlap with m at 3.65-3.78 ppm), 3.35-3.24 (m, 2H), 3.32 (s, 3H), 3.17 (s, 3H), 2.50 (´t´, $J$ = 7.3 Hz, 2H), 1.70-1.96 (m, 2H), 1.43 (s, 9H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 173.6, 156.5, 80.8, 75.6, 61.9, 61.0, 53.3, 32.7, 28.7, 27.4, 26.1; $[\alpha]_D^{25}$ +13.2 (*c* 2.3, $CHCl_3$).



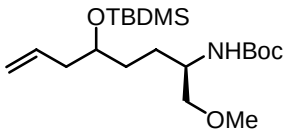

***tert*-Butyl (2*R*)-5-hydroxy-1-methoxyoct-7-en-2-ylcarbamate** (**5.57**)

i) Preparation of (*R*)-tert-butyl 1-methoxy-5-oxooct-7-en-2-ylcarbamate: A solution of allylmagnesiumbromide (1 M, 11.6 mL, 2.6 eq.) was dropwise added over 15 min. to a -78 °C cold solution of **(***R*)-*tert*-butyl 1-methoxy-5-(methoxy(methyl)amino)-5-oxopenta-2-ylcarbamate (**5.56**) (1.3 g, 4.48 mmol, 1.0 eq.) in THF (18 mL). The mixture was stirred at this temperature for 3½ h, diluted with Et2O (50 mL) and quenched (still at -78 °C) with aqueous 1 M $KHSO_4$ solution (25 mL). Partitioned between EtOAc (160 mL) and aqueous 1 M $KHSO_4$ solution (25 mL). The organic layer was washed with ½ saturated $NaHCO_3$ aqueous solution (60

mL), brine (50 mL) and dried ($Na_2SO_4$). Removal of the solvents under reduced pressure delivered (*R*)-*tert*-butyl 1-methoxy-5-oxooct-7-en-2-ylcarbamate (1.15 g, 95%) which was used immediately in the subsequent reaction.

ii) Preparation of *tert*-butyl (2*R*)-5-hydroxy-1-methoxyoct-7-en-2-ylcarbamate (**5.57**): To a solution of (crude) (*R*)-*tert*-butyl 1-methoxy-5-oxooct-7-en-2-ylcarbamate (1.15 g, 4.24 mmol, 1.0 eq.) in MeOH (23 mL) at 0 $^oC$ was (portionwise) added $NaBH_4$ (185 mg, 4.88 mmol, 1.15 eq.). The mixture was stirred at the same temperature of 45 min., quenched with saturated $NH_4Cl$ aqueous solution (7 mL), diluted with EtOAc (100 mL) and filtrated. The filtrate was washed with brine (2 portions of 50 mL), dried (Na2SO4) and concentrated under vacuum to afford the title compound as a pale yellow oil (1.14 g, 98%) which was used without further purification.

$R_f$ (hexane:EtOAc, 3:2 (v:v)) 0.18; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.62-5.86 (m, 1H), 4.88-5.11 (m, 2H), 4.69 (brs, 1H), (4.06 (m) and 3.52-3.74 (m), 2H), 3.24-3.33 (m, 5H), 2.04-2.2.27 (m, 2H), 1.29-1.54 (m, 13H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ (selected) 156.5, 142.3, 112.6, 79.2, 72.4, 69.8, 53.3, 51.0, 44.2, 32.5, 28.8, 26.3; $[\alpha]_D^{25}$ +14.6 (*c* 2.1, $CHCl_3$).



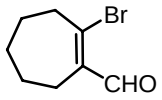

***tert*-Butyl (2*R*)-5-(*tert*-butyldimethylsilyloxy)-1-methoxyoct-7-en-2-ylcarbamate (5.58)**

i) Preparation of (7*R*)-7-amino-8-methoxyoct-1-en-4-ol hydrochloric salt: a solution of HCl (2 M in $Et_2O$, 6.0 mL, 5.0 eq.) was dropwise added to an ice cold solution of (crude) *tert*-butyl (2*R*)-5-hydroxy-1-methoxyoct-7-en-2-ylcarbamate (**5.57**) (625 mg, 2.29 mmol, 1.0 eq.) in $CH_2Cl_2$ (6.0 mL). After stirring at room temperature for 24 h, the solvents were removed under vacuum affording a light tan oil that was used directly in the next step (quantitative yield was assumed).

ii) Preparation of *tert*-butyl (2*R*)-5-(*tert*-butyldimethylsilyloxy)-1-methoxyoct-7-en-2-ylcarbamate (**5.58**): to a solution of the crude (7*R*)-7-amino-8-methoxyoct-1-en-4-ol hydrochloric salt and imidazole (760 mg, 11.16 mmol, 5 eq.) in DMF (5 mL) was added a solution of TBDMSCl (431.5 mg, 2.86 mmol, 1.25 eq.) in DMF (2 mL). After stirring at stirred at room temperature for 48 h (for convenience), the mixture was diluted with $CH_2Cl_2$ (100 ml), washed with 0.2 M $KHSO_4$ aqueous solution (2 portions of 20 mL), $H_2O$ (50 mL), "aqueous ½ saturated brine" (40 mL), dried ($Na_2SO_4$) and concentrated under vacuum. Purification by (short) flash chromatography ($CHCl_3$:MeOH 9:1, (v:v)) delivered the title compound as a faint

yellow oil (428 mg, 65% based on carbamate (**5.57**).

$R_f$ ($CHCl_3$:MeOH, 9:1 (v:v)) 0.20; $^1$H-NMR ($CDCl_3$, 300 MHz) (the two diastereomers are reported together) δ 5.75 (ddt, *J* = 7.3, 11.0, 17.8 Hz, 1H), 5.0 (´d´, *J* = 17.8 Hz, 1H) (partial overlap with ´d´at 4.9 ppm), 4.9 (´d´, *J* = 11.0 Hz, 1H) (partial overlap with ´d´at 5.0 ppm), 3.61-3.70 (m, 1H), 3.33-3.38 (m, 1H), 3.30 (s, 3H), 3.18 (td, J = 1.5, 7.5 Hz, 1H), 2..89-2.96 (m, 1H), 2.17 (´t´, J = 5.9 Hz, 2H), 1.32-1.57 (m, 4H), 0.84 (s, 9H), 0.00 (s, 6H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 139.5, 139.4, 121.4, 121.3, 76.4, 76.1, 63.4, 55.8, 55.7, 46.3, 46.1, 37.6, 37.4, 33.6, 33.1, 30.4, 22.6; $[\alpha]_D^{25}$ +18.4 (*c* 2.0, $CHCl_3$).




**(*Z*)-2-Bromo-cyclohept-1-enecarbaldeyhde** (**5.65**)

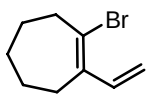
Procedure A: Following a literature procedure,[7.13] to an ice cold solution of $PPh_3$ (53.6 g, 0.2 mol, 2.3 eq.) in benzene (255 mL) was added $Br_2$ (10.5 mL, 0.2 mol, 2.3 eq.) dropwise over 15 min.. The yellow mixture obtained was allowed to reach room temperature and stirred for further 20 min., after which DMF (50.9 mL, 0.66 mol, 7.4 eq.) was added dropwise at room temperature over 15 min. After stirring for 1½ h, a solution of cycloheptanone (10.5 mL, 90 mmol, 1.0 eq.) in benzene (35 mL) was added dropwise at over 10 min., the pale yellow suspension obtained was stirred for 2 h and then refluxed for 3½ h. During reflux, a deep reddish color developed. After cooling to room temperature, the dark mixture was poured into iced-H2O (400 mL), stirred for 5 min., after which small portions of $Na_2CO_3$ were added until pH 8-9 was reached (approximately 26 g of $Na_2CO_3$ was used). After separation of the layers, the aqueous layer was extracted with benzene (3 portions of 100 mL) and the combined organic layers were washed with brine (120 mL), dried ($Na_2SO_4$) and concentrated under vacuum to a tan solid. Purification by bulb-to-bulb distillation at reduced pressure ($T_{oven}$ 75-80 °C, 0.2 mm.) delivered the title compound as a viscous pale yellow oil (14.3 g, 79%) which was kept in a frozen benzene matrix.

Procedure B: To an ice cold solution of DMF (14.4 mL; 225.7 mmol) in $CHCl_3$ (60 mL) was added dropwise freshly distilled $PBr_3$ (17.9 mL, 188.5 mmol) over a period of ½ h. The resulting suspension was stirred for 20 min. at 0 °C and 45 min further at room temperature. A solution of cycloheptanone (8.86 mL, 75.0 mmol) in $CHCl_3$ (30

[7.13] Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

mL) was added dropwise over a period of ½ h, resulting in an orange suspension which was refluxed for 3 h. On heating the mixture changes from a pale orange suspension to a clear red solution which grows darker until a blackish red solution was obtained. The solvent was removed by evaporation in vacuum affording a dark oily residue, which was very carefully quenched with iced $H_2O$ (150 mL) (note: this process is extremely exothermic!). The mixture was neutralized with solid $NaHCO_3$. The mixture was filtered and the aqueous layer extracted with $Et_2O$ (3 portions of 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (100 mL), $H_2O$ (100 mL), dried ($MgSO_4$) and evaporated in vacuum to afford the title compound as a viscous yellow oil (6.40 g, 42%) which was kept in a frozen benzene matrix.

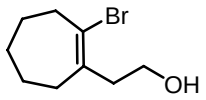
$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.71; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 9.92 (s, 1H), 2.98-3.05 (m, 2H), 2.47-2.51 (m, 2H), 1.76-1.84 (m, 2H), 1.1.62-1.69 (m, 2H), 1.41-1.49 (m, 2H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 193.5, 148.6, 140.7, 44.5, 31.6, 25.9, 25.4, 25.03.




**(*Z*)-1-Bromo-1-vinyl-cycloheptene** (**5.66**)

To an ice cold suspension of methyltriphenylphosphoniumbromide (25.2 g, 70.4 mmol, 1.1 eq.) in $Et_2O$ (210 mL) was dropwise added a solution of BuLi (1.6 M in hexanes, 44.0 mL, 1.1 eq.) over 25 min.. After stirring at room temperature for 15 min, the yellow suspension was refluxed for 4 h, cooled to room temperature and treated with a solution of (*Z*)-2-bromo-cyclohept-1-enecarbaldeyhde (**5.65**) (13.0 g, 64.0 mmol, 1.0 eq.) in $Et_2O$ (80 mL) over 20 min. The mixture was refluxed for 4 h and (for convenience) stirred at room temperature overnight. The suspension was filtered, the solid was rinsed with cold $Et_2O$ (3 portions of 100 mL). The combined filtrates were concentrated under vacuum to afford a deep tan oil which was filtered through a short column of silica (packed and eluted with $Et_2O$). The title compound was obtained as a yellow oil (9.1 g, 71%) which was used without further purification.

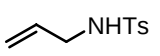
$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.76; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 6.74 (dd, $J$ = 17.3, 10.9 Hz, 1H), 5.19 (d, $J$ = 17.3 Hz, 1H), 5.08 (d, $J$ = 10.9 Hz, 1H), 2.76-2.82 (m, 2H), 2.31-2.36 (m, 2H), 1.66-1.74 (m, 2H), 1.38-1.55 (m, 4H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 138.9, 138.0, 127.9, 114.6, 42.0, 31.7, 28.1, 25.6, 25.4.




**(*Z*)-2-(2-Bromocyclohept-1-enyl)ethanol** (**5.67**)

To a solution of (*Z*)-1-bromo-1-vinyl-cycloheptene (**5.66**) (3.5 g, 17.3 mmol, 1.0 eq.) in THF (18 mL) was dropwise added a solution of 9-BBN (4.5 g, 18.2 mmol, 1.05 eq.) in THF (40 mL). The mixture was stirred at room temperature overnight and then carefully quenched with MeOH (16 mL). The mixture was cooled to ice bath temperature and treated sequentially with an aqueous 3 M NaOH solution (24 mL), and an aqueous 30% $H_2O_2$ solution (24 mL). The mixture was refluxed for 3½ h and cooled to room temperature. The aqueous layer was saturated with $K_2CO_3$ and the mixture extracted repeatedly with $Et_2O$ (4 portions of 50 mL).The organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated under vacuum. Purification by flash chromatography (hexane:$Et_2O$ 1:3, (v:v)) followed by bulb-to-bulb distillation at reduced pressure ($T_{oven}$ 110-110 $^oC$, 0.2 mm.) delivered the title compound as a colorless oil (3.2 g, 83%).

$R_f$ (hexane:EtOAc, 3:1 (v:v)) 0.14; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 6.72 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.19 (dd, *J* = 1.2, 17.3 Hz, 1H), 5.08 (dd, *J* = 1.2, 10.9 Hz, 1H), 3.61 (´q´, *J* = 6.0, 6.7 Hz, 2H), 2.44 (t, *J* = 6.7 Hz, 2H), 2.29-2.33 (m, 2H), 2.20-2.32 (m, 2H), 1.64-1.73 (m, 2H), 1.35-1.47 (m, 4H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 138.6, 124.6, 60.6, 43.5, 41.5, 33.9, 31.7, 25.9, 25.7.

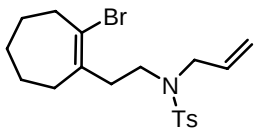



***N*-Allyl-4-methylbenzenesulfonamide** (**5.68**)

Following a literature procedure,[7.1] an aqueous solution of NaOCl (12% in weight, 32.5 g of solution, 52.5 mmol, 1.5 eq.) was added dropwise over 1 h to a chilled solution of allylamine (2.63 mL, 35.0 mmol, 1.0 eq.), acetic acid (2.0 mL; 35.0 mL, 1.0 eq.) and sodium benzenesulfinate (12.47 g, 70 mmol, 2.0 eq.) in H2O (155 mL). The resulting mixture was stirred at room temperature overnight, recooled to 0 $^oC$, acidified to pH 1 with a 1M HCl aqueous solution (approximately 80 mL used), stirred for 10 min. The title compound was obtained by filtration and dried in a vacuum desiccator (6.58 g, 89%).

Mp 61-62 $^oC$ (lit.[7.1] 62-64 $^oC$); $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.76 (´d, *J* = 8.4 Hz, 2H), 7.31 (´d´, *J* = 8.4 Hz), 5.65-5.78 (m, 1H), 5.07-5.20 (m, 2H), 4.62 (brt, *J* = 6.1 Hz), 3.58 (tt, *J* = 1.5, 5.8 Hz), 2.43 (s, 3H).

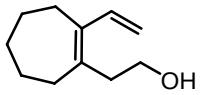
[7.1] Scully Jr., F. E.; Bowdring, K. *J. Org. Chem.* **1981**, *46*, 5077.




**(*Z*)-*N*-Allyl-*N*-(2-(2-bromocyclohept-1-enyl)ethyl)-4-methylbenzenesulfonamide** (**5.69**)

To an ice cold solution of (*Z*)-2-(2-bromocyclohept-1-enyl)ethanol (**5.67**) (1.0 g, 4.56 mmol, 1.0 eq.), $PPh_3$ (2.99 g, 11.4 mmol, 2.5 eq.) and *N*-Allyl-4-methylbenzenesulfonamide (**5.68**) (1.25 g, 5.93 mmol, 1.3 eq.) in THF (25 mL) was added dropwise DIAD (1.84 g, 9.12 mmol, 2.0 eq.) over 1 h. The solution obtained was stirred at room temperature for 26 h (for convenience), after which the solvent was removed under vacuum to afford a light tanned oil. Purification by flash chromatography (hexane:$Et_2O$, 3:1 (v:v)) afforded the title compound as colorless viscous oil (1.3 g, 70 %).

$R_f$ (hexane:EtOAc, 2:1 (v:v)) 0.60; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.71 (´d´, *J* = 8.3 Hz, 2H), 7.30 (´d´, *J* = 8.3 Hz, 2H), 5.60-5.73 (m, 1H), 5.23 (d´q´, *J* =1.4, 17.1 Hz, 1H), 5.16 (d´q´, *J* = 1.4, 10.0 Hz, 1H), 3.85 (d, *J* = 6.5 Hz, 2H), 3.13-3.18 (m, 2H), 2.67-2.70 (m, 2H), 2.42 (d, *J* = 7.5 Hz, 2H) (overlap with s at 2.42 ppm), 2.42 (s, 3H) (overlap with t at 2.42 ppm), 2.20-2.23 (m, 2H), 1.67-1.75 (m, 2H), 1.43-1.58 (m, 4H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 143.4, 138.5, 137.5, 133.2, 129.9, 127.4, 124.5, 119.4, 50.8, 44.4, 41.3, 39.6, 34.0, 31.5, 25.9, 25.7, 21.8.

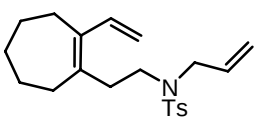



**(*Z*)-2-(2-vinylcyclohept-1-enyl)ethanol**

To a suspension of (*Z*)-2-(2-bromocyclohept-1-enyl)ethanol (**5.67**) (850 mg, 3.88 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (314 mg, 0.27 mmol, 7 mol%) in THF (5.7 mL) was dropwise added a solution of vinyl bromide (1 M in THF, 10.2 mL, 2.6 eq.) at room temperature. The mixture was gently refluxed for 3h 45 min. The resulting solution was recooled to 0 $^{o}$C, carefully quenched with saturated $NH_4Cl$ aqueous solution (5 mL) and diluted with $Et_2O$ (25 mL). The aqueous layer was extracted with $Et_2O$ (2 portions of 5 mL). The combined organic layers were washed with brine (10 mL), dried ($Na_2SO_4$) and the solvents removed under vacuum. Purification of the obtained residue by flash chromatography (hexane:$Et_2O$, 1:1 (v:v)) delivered the title compound (546 mg, 84%, with a minor impurity)

$R_f$ (hexane:$Et_2O$ 1:1 (v:v)) 0.24; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 6.78 (dd, *J* = 11.0, 17.2 Hz, 1H), 5.19 (dd, *J* = 1.0, 17.2 Hz, 1H), 5.01 (dd, *J* = 1.0, 11.0, 1H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.51 (t, *J* = 6.3 Hz, 2H), 2.36-2.39 (m, 2H), 2.27-2.30 (m, 2H), 1.41-1.51 (m, 2H), 1.70-1.79 (m, 4H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 139.2, 138.5, 138.2, 115.7,

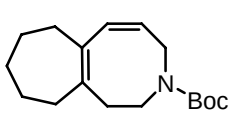
61.4, 37.0, 33.2, 33.1, 32.8, 28.2, 27.9.




**(*Z*)-*N*-Allyl-4-methyl-*N*-(2-(2-vinylcyclohept-1-enyl)ethyl)benzenesulfonamide** (**5.71**)

To an ice cold solution of (*Z*)-2-(2-vinylcyclohept-1-enyl)ethanol (100 mg, 0.60, 1.0 eq.), $PPh_3$ (394 mg, 1.5 mmol, 2.5 eq.) and *N*-Allyl-4-methylbenzenesulfonamide (**5.68**) (172 mg, 0.81 mmol, 1.35 eq.) in THF (4 mL) was added dropwise DIAD (243 mg, 1.2 mmol, 2.0 eq.) over 1 h. The solution obtained was stirred at room temperature for 26 h (for convenience), after which the solvent was removed under vacuum to afford a light tanned oil. Purification by flash chromatography (hexane:$Et_2O$, 3:1 (v:v)) afforded the title compound as colorless viscous oil (1.3 g, 70 %).

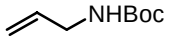
$R_f$ (hexane:$Et_2O$, 3:1 (v:v)) 0.40; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.70 (´d´, *J* = 8.0 Hz, 2H), 7.29 (´d´, *J* = 8.0 Hz, 2H), 6.59 (dd, *J* = 10.9, 17.1 Hz, 1H), 5.57-5.76 (m, 1H), 4.95-5.24 (m, 4H), 3.83 (d, *J* = 6.5 Hz, 2H), 3.04-3.10 (m, 2H), 2.38-2.43 (m, 5H; includes a s at 2.42 ppm corresponding to 3H), 2.27-2.30 (m, 2H), 2.18-2.22 (m, 2H), 1.66-1.75 (m, 2H), 1.36-1.47 (m, 4H). $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 143.0, 139.1, 138.6, 137.9, 137.1, 133.9, 28.2, 127.8, 116.3, 115.9, 51.4, 51.2, 33.1, 33.0, 31.8, 28.3, 28.0,25.7 21.2.




**(5*Z*,6a*Z*)-*tert*-butyl 1,2,8,9,10,11-hexahydro-4*H*-cyclohepta[*d*]azocine-3(*7H*)-carboxylate** (**5.74**)

A mixture of (*Z*)-*N*-Allyl-4-methyl-*N*-(2-(2-vinylcyclohept-1-enyl)ethyl)benzenesulfonamide (**5.71**) (80 mg, 0.22 mmol, 1.0 eq.) and 2$^{nd}$ generation Grubbs catalyst (25 mg, 0.029 mmol, 13 mol%) in degassed $CH_2Cl_2$ (37 mL) was refluxed under argon for 3 h, after which time an aqueous solution of $P(CH_2OH)_3$ (1.5 M, 0.48 mL, 25 eq.) was added and the resulting biphasic system was further refluxed overnight. The mixture was washed with $H_2O$ (15 mL) and the aqueous layer extracted with $CH_2Cl_2$ (8 mL). The combined organic layers were washed with brine (25 mL), dried ($Na_2SO_4$) and the solvent was removed under vacuum to afford a yellow residue. Purification by flash chromatography (hexane:$Et_2O$, 3:1 (v:v); demetallated silica gel) delivered the title compound as a viscous colorless oil (46 mg, 62%).

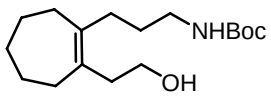
$R_f$ (hexane:$Et_2O$, 3:1 (v:v)) 0.29; $^1$H-NMR ($CDCl_3$, 200 MHz) δ 7.75 (´d´, 2H), 7.35 (´d´, 2H), 5.93 (d, 1H), 5.48-5.59 (m, 1H), 3.44-3.52 (brs, 2H), 3.15 (t, 2H), 2.42 (s, 3H), 1.19-2.23 (m, 12H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 143.6, 138.6, 137.1, 136.2, 129.8, 128.0, 127.3, 123.2, 46.4, 43.7, 37.2, 35.8, 33.0, 32.5, 26.7, 26.3, 21.7.




***tert*-Butyl allylcarbamate** (**5.75**).

Following a literature procedure,[7.2] to an ice cold solution of allylamine (2.3 mL, 30.6 mmol, 1.0 eq.) in $CH_2Cl_2$ (45 mL) was portionwise added a solution of $Boc_2O$ (6.68 g, 30.6 mmol, 1.0 eq.) in $CH_2Cl_2$ (5 mL). The resulting solution was stirred overnight at room temperature, diluted with $CH_2Cl_2$ (40 mL) and washed with aqueous 5% citric acid solution (2 portions of 50 mL), $H_2O$ (25 mL), brine (25 mL), dried (Na2SO4) and the solvent removed under vacuum to afford a white solid. Recrystallization from (hot) hexane (8 mL) delivered the title compound as white crystals (3.1 g, 67%).

$R_f$ (hexane:EtOAc 2:1 (v:v)) 0.39; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 5.70-5.71 (m, 1H), 5.11 (dq, *J* = 1.6, 17.2 Hz, 1H), 5.04 (dq, *J* = 1.6, 10.2 Hz, 1H), 4.55 (brs, 1H), 3.65 (brt, *J* = 4.9 Hz, 2H), 1.38 (s, 9H).

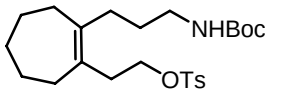



**(*Z*)-tert-Butyl 3-(2-(2-hydroxyethyl)cyclohept-1-enyl)propylcarbamate** (**5.76**)

To an ice cold solution of *tert*-butyl allylcarbamate (**5.75**) (1.6 g, 10.2 mmol, 1.5 eq.) in THF (41 mL) was dropwise added a solution of 9-BBN (0.5 M in THF, 27.4 mL, 2.0 eq.) and the resulting solution was stirred at room temperature for 20 h. The reaction flask was covered with silver foil and an aqueous solution of $K_3PO_4$ (3 M, 4.70 mL, 2.05 eq.), a solution of (*Z*)-2-(2-bromocyclohept-1-enyl)ethanol (5.??) (1.5 g, 6.8 mmol, 1.0 eq.) in degassed DMF (57 mL) and $PdCl_2$(dppf) (320 mg, 6% molar) were sequentially added and the resulting mixture was stirred at room temperature overnight. Partitioned between ½ saturated $NaHCO_3$ aqueous solution (300 mL) and $Et_2O$ (300 mL), the aqueous layer was extracted with $Et_2O$ (2 portions of 60 mL). The combined organic layers were washed with brine (200 mL), dried ($Na_2SO_4$) and the solvent was removed under reduced pressure affording a tan residue. Purification by flash chromatography (hexane:EtoAc, 1:1 (v:v)) delivered the title compound as a viscous pale yellow oil (1.9 g, 95%).

[7.2] Rocheblave, L.; Bihel, F.; De Michelis, C.; Priem, G.; Courcambeck, J.; Bonnet, B.; Chermann, J.-C.; Kraus, J.-L. J. Med. Chem. 2002, 45, 3321.

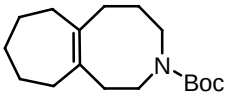
$R_f$ (hexane:EtOAc 1:1 (v:v)) 0.35; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 4.67 (brs, 1H), 3.62 (t, *J* = 6.7 Hz, 2H), 3.09 (brq, *J* = 5.6 Hz, 2H), 2.30 (t, 6.7 Hz, 2H), 2.03-2.14 (m, 6H), 1.81 (brs, 1H), 1.66-1.75 (m, 2H), 1.40-1.54 (m, 15H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 156.3, 139.8, 133.2, 79.3, 60.9, 40.8, 38.2, 34.1, 33.9, 32.9, 32.3, 28.9, 28.7, 27.2, 27.1.




**(*Z*)-2-(2-(3-(tert-Butoxycarbonylamino)propyl) cyclohept-1-enyl)ethyl 4-methybenzenesulfonate**

A solution of (*Z*)-tert-butyl 3-(2-(2-hydroxyethyl)cyclohept-1-enyl)propylcarbamate (**5.76**) (250 mmg, 0.84 mmol, 1.0 eq.), $NEt_3$ (0.23 mL, 1.68 mmol, 2.0 eq.), DMAP (12 mg,0.1 mmol, 0.1 eq), TsCl (195 mg, 1.0 mmol, 1.2 eq.) in $CH_2Cl_2$ (3 mL) was stirred overnight at room temperature. The mixture was partitioned between $Et_2O$ (30 mL) and 0.5 M HCl aqueous solution (15 mL). The organic layer was washed with 0.5 M HCl aqueous solution (15 mL), $H_2O$ (15 mL), brine (15 mL), dried ($Na_2SO_4$) and the solvent was removed under vacuum. The residue obtained was purified by flash chromatography (hexane:Et2O 1:2, (v:v)) to afford the title compound as a colorless oil (305 mg, 80%).

$R_f$ (hexane:EtOAc, 1:1 (v:v)) 0.45; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 7.78 (´d´, *J* = 8.3 Hz, 2H), 7.34 (´d´, *J* = 8.3 Hz, 2H), 4.56 (brs, 1H), 3.98 (t, *J* = 7.2 Hz, 2H), 3.00-3.11 (m, 2H), 2.45 (s, 3H), 2.36 (t, *J* = 7.2 Hz, 2H), 1.91-2.09 (m, 6H), 1.60-1.70 (m, 2H), 1.44 (s, 9H), 1.24-1.40 (m, 6H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 156.2, 144.9, 140.7, 133.4, 131.0, 130.0, 128.1, 79.2, 69.0, 40.8, 34.8, 34.1, 34.1, 32.7, 32.5, 28.9, 28.7, 26.9, 26.8, 21.9.

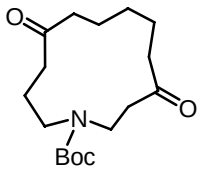



**(*Z*)-*tert*-Butyl 1,2,5,6,8,9,10,11-octahydro-4*H*-cyclohepta[*d*]azocine-3(7*H*)-carboxylate** (**5.77**)

A solution of (Z)-2-(2-(3-(tert-butoxycarbonylamino)propyl)cyclohept-1-enyl)ethyl 4-methybenzenesulfonate (300 mg, 0.66 mmol, 1.0 eq.) in THF (9 mL) was dropwise added to an ice cold suspension of (pentane washed) NaH (115 mg of a 60% NaH dispersion in oil, corresponding to 65 mg NaH, 2.9 mmol, 4.3 eq.) in THF (28 mL). The resulting mixture was refluxed over 3½ h, recooled to 0 °C, carefully quenched with a saturated $NH_4Cl$ aqueous solution (5 mL) and extracted with a pentane:$Et_2O$ 1:1 (v:v) solution (2 portions of 60 mL). The combined organic layers were washed with brine (20 mL), dried ($Na_2SO_4$) and the solvents were removed under vacuum. The residue obtained was purified by flash chromatography (pentane:$Et_2O$, 2:1 (v:v);

demetallated silica gel). The title compound was obtained as a colorless oil (132 mg, 72%).

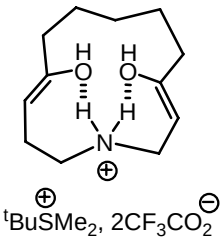
$R_f$ (hexane:$Et_2O$, 1:2 (v:v)) 0.68; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 3.26-3.48 (m, 2H), 3.09-3.26 (m, 2H), 2.02-2.29 (m, 8H), 1.61-1.81 (m, 4H); 1.38-1.56 (m, 13H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 155.2, 131.7, 130.4, 79.4, 49.2, 48.3, 33.7, 32.5, 32.2, 31.8, 28.6, 28.5, 29.0, 27.3, 26.6.




**_tert_-Butyl 4,10-dioxoazacyclotridecane-1-carboxylate** (**5.78**)

A solution of (*Z*)-*tert*-Butyl 1,2,5,6,8,9,10,11-octahydro-4*H*-cyclohepta[*d*]azocine-3(7*H*)-carboxylate (**5.77**) (60 mg, 0.21 mmol, 1.0 eq.) in $CH_2Cl_2$ (4 mL) and MeOH (1.3 mL) was cooled to -78 $^o$C and $O_3$ was bubbled until a persistent pale blue color was seen (typically 15 min.). Argon was then bubbled for 5 min., DMS (79 μL, 1.1 mmol, 5 eq.) was added and stirring continued at the same temperature for 10 min. The reaction was allowed to warm to room temperature over 2 h, partitioned between $CH_2Cl_2$ (10 mL) and aqueous ½ saturated brine (10 mL). The organic layer was dried ($Na_2SO_4$), the solvent removed under vacuum affording a colorless oil (67 mg, quantitative).

$R_f$ (hexane:$Et_2O$, 1:2 (v:v)) 0.17; $^1$H-NMR ($CDCl_3$, 300 MHz) δ 3.40 (t, *J* = 5.8 Hz, 2H), 3.17 (t, *J* = 6.3 Hz, 2H), 2.68 (t, *J* = 5.8 Hz, 2H), 2.32-2.41 (m, 4H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.52-1.73 (m, 6H), 1.4 (s, 9H), 1.24 (´quint´, *J* = 6.9 Hz, 2H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 212.5, 210.6, 156.4, 80.1, 49.1, 44.3, 42.7, 42.1, 41.9, 38.5, 28.7, 26.8, 23.9, 23.3, 22.3.




**Salt** (**5.79**)

A solution of *tert*-butyl 4,10-dioxoazacyclotridecane-1-carboxylate (**5.78**) (20 mg, 0.064 mmol, 1.0 eq.), TFA (95 μL, 1.24 mmol, 19.4 eq.), $SMe_2$ (50 μL, 0.69 mmol, 10.8 eq.) in CH2Cl2 (0.5 mL) was stirred at 0 $^o$C for 2 h and 24 h at room temperature. The solution was diluted with toluene (25 mL) and concentrated under vacuum to approximately 1/5 of its initial volume, after which this procedure was repeated. Removal of the solvent under reduced pressure delivered the crude salt (**5.79**) (38 mg).

$^{1}$H-NMR ($CDCl_3$, 200 MHz) δ 11.0 (brs, 2H), 4.15 (brt, 2H), 3.85 (t, 2H), 3.15 (t, 2H), [2.8 (s, 6H) (from $^{t}BuS^{+}Me_2$)], 2.80 (t, 2H), 2.10-2.50 (m, 6H), 1.65-1.85 (m, 4H), [1.60 (s, 9H) (from $^{t}BuS^{+}Me_2$)]; $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 178.3, [160.1,160.9, 160.1, 159.4], 157.0, 122.5, 118.9, 113.1, 58.5, 54.1, 43.4, 34.6, 30.7,

**Apendix I**

List of Publications

Appendix I

(1) **Vital, P.**; Tanner, D. “Efficient and Highly Enantioselective Formation of the All-Carbon-Quaternary Stereocentre of Lyngbyatoxin A”, *Org. Biomol. Chem.* **2006**, *4*, 4292-4298.

# Efficient and highly enantioselective formation of the all-carbon quaternary stereocentre of lyngbyatoxin A

**Paulo Vital and David Tanner***

***Received 31st August 2006, Accepted 27th September 2006***
***First published as an Advance Article on the web 20th October 2006***
**DOI: 10.1039/b612578f**

Indole **25**, an advanced intermediate in a projected enantioselective total synthesis of lyngbyatoxin A **1**, was prepared from allylic alcohol **11** in 9 steps and >95% ee, key transformations being the enantiospecific rearrangement of vinyl epoxide **14** and the Hemetsberger–Knittel reaction of azide **24**.

## Introduction

The Hawaiian blue–green alga *Lyngbya majuscula* Gomont is implicated in the occasional outbreaks of a severe contact dermatitis commonly known as "swimmers' itch".[1] One of the causative agents for this condition is lyngbyatoxin A **1** (Fig. 1), an alkaloid first isolated in 1979 by Moore and co-workers from the lipid extract of seaweed.[2]

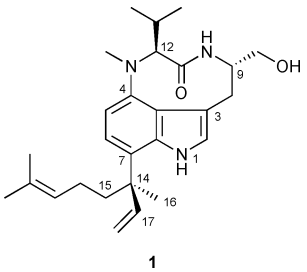
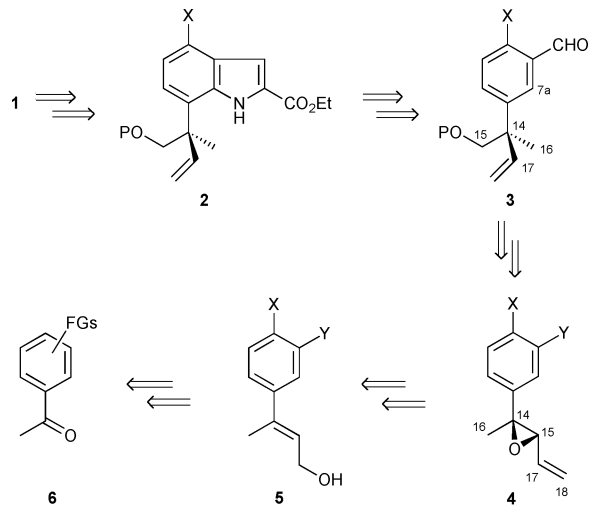


**Fig. 1** Structure of lyngbyatoxin A.

Lyngbyatoxin A is also a potent tumor promoter[3] and, like other indolactam alkaloids, exerts its biological activity through activation of protein kinase C (PKC), a family of phosphorylating enzymes involved in the regulation of important cellular processes.[4] Investigation of the structural requirements for the selective activation/inhibition of each PKC isotype is currently an important goal in pharmaceutical research.[5] This interesting biological profile combined with a challenging molecular structure makes lyngbyatoxin A and its analogues worthy targets for the synthetic community.[5,6]

A critical step in any enantioselective approach towards lyngbyatoxin A concerns the installation of the quaternary carbon at C-14.[7,8] We have previously addressed this issue by means of the Jung rearrangement[9] of chiral vinyl epoxides carrying an indole moiety, but this approach was plagued by substantial loss of enantiomeric purity during the rearrangement step.[10] Herein we report a successful (>95% ee) "second generation" approach to this problem, involving epoxide rearrangement *prior* to formation of the indole unit.

According to the simplified retrosynthetic analysis shown in Scheme 1, the target molecule was envisioned to arise from indole **2** *via* functional group manipulation. Key intermediate **2** would be obtained from aldehyde **3** by means of a Hemetsberger–Knittel reaction,[11] while the quaternary carbon stereocentre was planned to be accessed *via* the enantiospecific Jung rearrangement[9] of chiral vinyl epoxide **4**, itself available from allylic alcohol **5** by means of the Sharpless asymmetric epoxidation reaction;[12] a suitably functionalised acetophenone **6** was to be the starting point for the synthesis.



**Scheme 1** Simplified retrosynthetic analysis for lyngbyatoxin A.

## Results and discussion

After considerable experimentation to determine which functional groups on the aromatic ring would be compatible with the above strategy, the combination X = Br, Y = I (Scheme 1) was chosen.

Since the quaternary centre was planned to be installed by a "chirality transfer" process, the enantiomeric purity of the starting vinyl epoxide is critical, and this was the first issue to be addressed (Scheme 2).

Following a literature procedure,[13] *p*-aminoacetophenone **7** was treated with ICl to afford the corresponding iodinated aniline **8** in good yield. Amine–halogen exchange was then accomplished under Sandmeyer conditions[14] ($NaNO_2$ followed by CuBr, in conc. HBr) to deliver ketone **9** in 86% yield. A Horner–Wadsworth–Emmons reaction[15] with the sodium salt of

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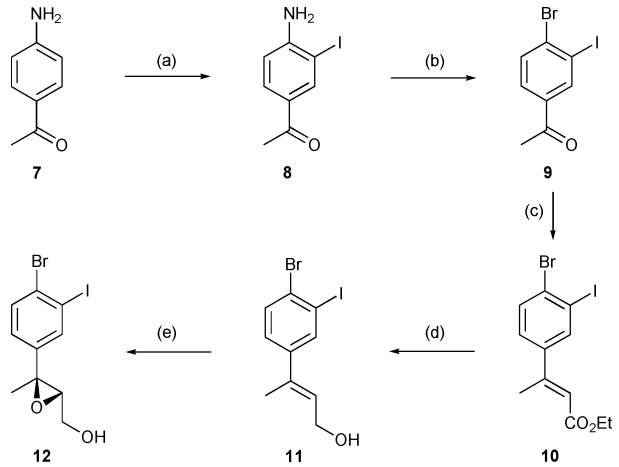
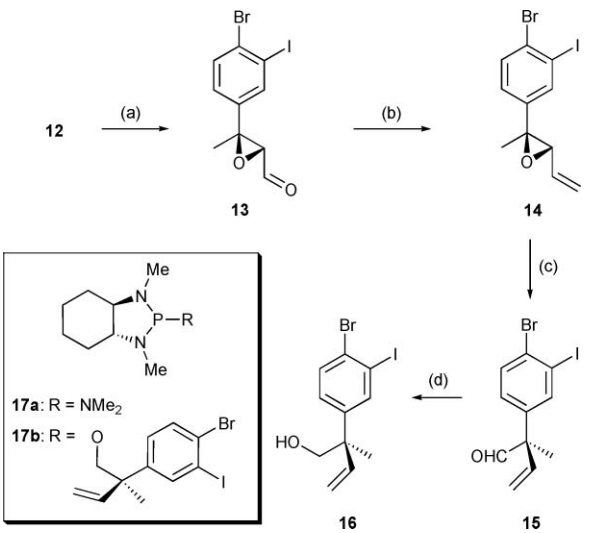


**Scheme 2** *Reagents and conditions*: (a) ICl, $CaCO_3$ aq., MeOH, rt, 86%; (b) $NaNO_2$ aq., HBr conc., −10 °C to 0 °C, then CuBr, HBr conc., 80 °C, 86%; (c) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 0 °C to rt, 64%; (d) DIBAL, $Et_2O$, 0 °C to rt, 96%; (e) L-(+)-DET, 4 Å MS, $Ti(O^iPr)_4$, $^t$BuOOH, $CH_2Cl_2$, −20 °C; quant. (crude), 92–94% ee.

triethylphosphonoacetate delivered a mixture of the corresponding $E$ : $Z$ α,β-unsaturated esters in an unoptimised 3.7 : 1 ratio. These isomers could be separated easily by flash chromatography, allowing the isolation of pure *E*-unsaturated ester **10** in 64% yield. Reduction of the ester functionality with DIBAL proceeded uneventfully, providing allylic alcohol **11** in excellent yield. We were then pleased to find that the key asymmetric epoxidation step[12] delivered **12** as a highly crystalline product in essentially quantitative yield and with 92–94% ee, as determined by chiral HPLC. A single recrystallisation from hot hexane–$Et_2O$ 2 : 1 (v : v) yielded material which was enantiomerically pure within the limits of detection.

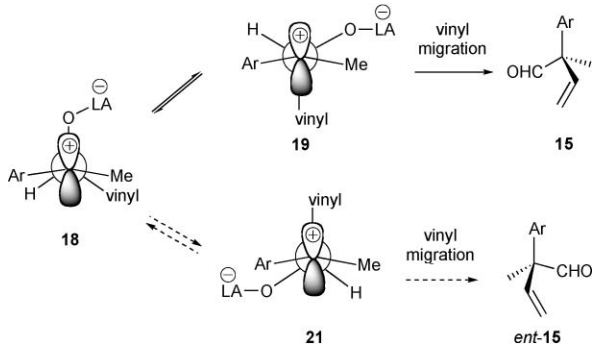
Having secured our first chiral intermediate, we proceeded to investigate the installation of the all-carbon quaternary centre of the target (Scheme 3).[8]



**Scheme 3** *Reagents and conditions*: (a) $(COCl)_2$, DMSO then $Et_3N$, $CH_2Cl_2$, −78 °C; (b) $Ph_3PCH_3Br$, KHMDS, THF, 0 °C; (c) $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, −78 °C, 52% (based on **12**); (d) $NaBH_4$, MeOH, 0 °C to rt, 81%.

Conversion of allylic epoxide **12** to vinyl epoxide **14** was accomplished using the conditions previously reported[9,10] for this type of substrate. Swern oxidation[16] of **12** delivered epoxy aldehyde **13**, which upon Wittig reaction[17] with KHMDS as base gave **14**. Due to the lability of compounds **13** and **14**, these were either used directly or submitted to rapid filtration through a short column of silica gel. Subjection of vinyl epoxide **14** to the conditions developed by Jung for the rearrangement reaction[9] ($BF_3{\cdot}Et_2O$, $CH_2Cl_2$, −78 °C) delivered aldehyde **15** as the sole product in 52% yield based on **12**. Aldehyde **15** was not suitable for prolonged storage, even at low temperature, so it was routinely subjected to $NaBH_4$ reduction to the corresponding primary alcohol **16**. To determine if the rearrangement had proceeded with complete 1,2-chirality transfer, alcohol **16** was derivatized with the Alexakis reagent **17a**[18] to the phosphorous adduct **17b**. Whereas the $^{31}$P-NMR spectrum of racemic **17b**, prepared by MCPBA epoxidation of **11** followed by an identical sequence of steps, showed two peaks of equal intensity at 139.0 and 138.8 ppm, only the higher-field peak was present for **17b** produced *via* the Sharpless epoxidation.

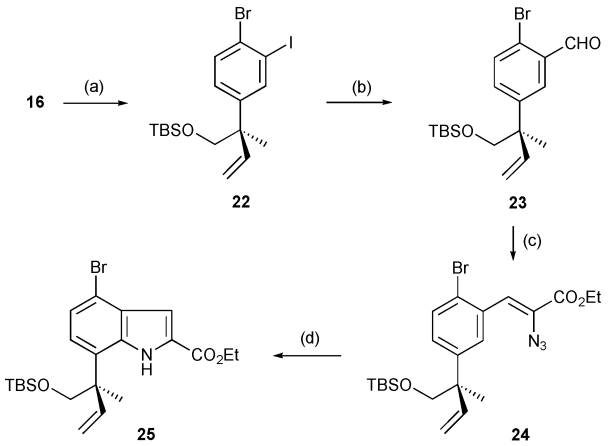
This result implies that the desired vinyl migration in conformer **19**, where the migrating group is correctly aligned with the adjacent vacant p orbital, proceeds significantly faster than conformer equilibration. The latter process would result in the population of conformer **21**, thus leading to vinyl migration onto the enantiotopic face of the planar carbocation and in the undesired formation of *ent*-**15** (Scheme 4).



**Scheme 4** Intermediate **18** is formed from **14** and $BF_3{\cdot}Et_2O$, giving **15** *via* conformer **19**.

With the quaternary centre installed in an enantioselective manner, we then attended to the construction of the indole nucleus (Scheme 5).[19]

Treatment of the (crude) primary alcohol **16** with TBSCl and imidazole[20] delivered silyl ether **22** in 80% yield based on **15**. Our annelation strategy calls for a benzaldehyde derivative, and we planned to introduce the required formyl group *via* a regio- and chemo-selective halogen–lithium exchange.[21] Somewhat unexpectedly, this step proved to be very problematic. When the standard conditions for this transformation were used (BuLi, DMF, THF–$Et_2O$ or THF, −100 °C or −78 °C, respectively), only a complex mixture, containing at best trace amounts of the expected aldehyde **22**, was obtained. After extensive model studies with *o*-bromoiodobenzene, we eventually found that when the reaction was carried out in toluene at approximately −100 °C the competing benzyne formation was comparatively slow, and thus the initially formed lithiated species could be successfully trapped




**Scheme 5** (a) TBSCl, imid., DMF, rt, 80% (based on **15**); (b) BuLi then DMF, PhMe, approx. −100 °C, 65–71%; (c) $N_3CH_2CO_2Et$, NaOEt, EtOH, −15 °C to −10 °C, 60%; (d) xylene, 140 °C, 69%.

with DMF.[22] Using these conditions, aldehyde **23** was finally obtained reproducibly in 65–71% yield. Subsequent NaOEt-promoted condensation with excess ethyl azidoacetate at low temperature afforded azide **24** in 60% yield, thus setting the stage for the planned Hemetsberger–Knittel reaction.[11] This was accomplished by heating **24** in xylene, which smoothly furnished indole **25** in 69% yield.

Indole **25** is conveniently functionalised so as to allow its conversion into lyngbyatoxin A: the C-3 indolic position is intrinsically nucleophilic,[23] whereas the bromine at C-4 provides a suitable handle for insertion of the amino functionality;[24] furthermore, the TBDMS-protected alcohol moiety will allow the construction of the linalyl appendage (Fig. 2).

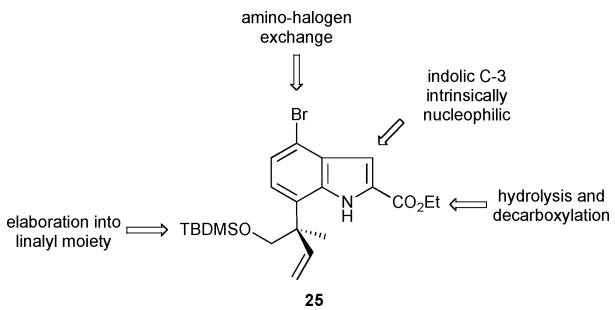



**Fig. 2** Planned manipulations to convert indole **25** into lyngbyatoxin A.

## Conclusion

The synthesis of enantiomerically pure indole **25**, a late key intermediate in the enantioselective total synthesis of lyngbyatoxin A, was accomplished in 9 steps from the readily available allylic alcohol **11**. The salient features of this route are (i) Sharpless asymmetric epoxidation for initial introduction of chirality, (ii) completely enantiospecific Jung rearrangement of chiral epoxide **14** to install the all-carbon quaternary centre of the target molecule, (iii) formylation of **22** *via* chemo- and regio-selective halogen–lithium exchange, and (iv) clean formation of the indole nucleus through the Hemetsberger–Knittel reaction. To the best of our knowledge, this is the first example of stereocontrolled generation of the characteristic all-carbon quaternary centre of lyngbyatoxin A, thus solving a long-standing problem in the synthesis of this biologically significant alkaloid.

## Experimental

### General

All moisture- and air-sensitive reactions were carried out under an argon atmosphere using oven-dried or flame-dried glassware. Reaction solvents were distilled prior to use by standard procedures. $Et_2O$, THF and toluene were distilled under nitrogen from sodium benzophenone. $CH_2Cl_2$ and $NEt_3$ were distilled under nitrogen from $CaH_2$. Anhydrous DMSO and DMF were purchased from Aldrich and stored over 4 Å molecular sieves, under argon. $^1$H-NMR (300 MHz and 500 MHz) and $^{13}$C-NMR (75 MHz) spectra were recorded on either a Varian Mercury 300 (300 MHz) or a Varian Inova 500 (500 MHz) spectrometers at ambient temperature. $^{31}$P-NMR (202 MHz) spectra were recorded on a Varian Inova 500 (500 MHz) spectrometer at ambient temperature. Chemical shifts ($\delta$) are reported in ppm. Undeuterated solvent residues were used as internal standard ($CHCl_3$, $^1$H: 7.27 ppm and $^{13}$C: 77.0 ppm). $H_3PO_4$ (30% aq., 0.0 ppm) was used as external standard for $^{31}$P-NMR. Coupling constants ($J$) are given in Hertz (Hz). Optical rotations were measured with a Perkin Elmer 241 polarimeter at ambient temperature, and the concentration ($c$) is given in g per 100 mL. Analytical high performance liquid chromatography (HPLC) was performed using a Varian 9012 solvent delivery system with a Varian 9065 polychrome diode array detector. HPLC grade solvents were obtained from LAB-SCAN. Electron impact (EI) low resolution mass spectra (LRMS) were performed with a VG Trio-2 single quadrupole instrument at the Department of Chemistry, Technical University of Denmark. Melting points of crystalline materials were determined on a Heidolph capillary melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) analyses were performed using 0.25 mm Merck Kieselgel aluminium-backed 60 F254 silica gel plates. Visualization was achieved by i) exposure to UV light, ii) brief exposure to iodine vapors, iii) dipping into a solution of 5–10% of phosphomolybdic acid in EtOH, and iv) gentle heating. Merck silica gel 60 (40–63 μm, 230–400 mesh) was used for flash chromatography purification. Preparative thin layer chromatography (PTLC) was performed on 20 × 20 cm, 1500 μm glass-backed plates with fluorescent indicator (Aldrich). Microanalyses were performed at the Microanalysis Laboratory, Institute of Physical Chemistry, University of Vienna, Austria. Molecular sieves were dried at 150–160 °C for at least 12 h and then allowed to reach room temperature under argon. Unless otherwise stated, commercially available reagents, purchased from Aldrich, Fluka or Merck, were used without further purification. "Aqueous $\frac{1}{2}$ saturated brine" and "aqueous $\frac{1}{3}$ saturated $NaHCO_3$" refer to a water–brine, 1 : 1 (v : v) and water–saturated $NaHCO_3$, 2 : 1 (v : v) solutions, respectively. The following cooling baths were used: ether–liquid nitrogen (*ca.* −110 to −85 °C); acetone–dry ice (typically for −78 °C but also for temperatures above); *ortho*-dichlorobenzene–liquid nitrogen (*ca.* −25 °C). Commercial NaH (as a 60% dispersion in oil) was washed with pentane (2 portions that cover the amount of NaH dispersion used), and the last traces of pentane were removed under high vacuum.

**4-Bromo-3-iodoacetophenone (9).** i) Preparation of the diazonium salt. To a suspension of 4-acetyl-2-iodoaniline **8**[13] (8.45 g, 32.3 mmol) in aqueous 47% HBr (77 mL) at −10 °C was added dropwise, over 15 min, a solution of $NaNO_2$ (2.65 g, 38.0 mmol, 1.18 eq.) in water (35 mL). The deep-tan mixture obtained was stirred for 10 min at this temperature, after which the temperature was allowed to increase from −5 °C to 0 °C and stirring continued for a further 1.5 h. The obtained mixture was then kept at ice bath temperature. ii) Sandmeyer reaction. To a vigorously stirred (purple) mixture of CuBr (5.57 g, 38.8 mmol, 1.2 eq.) in aqueous 47% HBr (42 mL) at 60 °C was added portion-wise, over 50 min, the above diazonium suspension (caution: significant frothing occurred during additions), after which the temperature was increased to 80 °C and stirring continued for a further 25 min. The resulting dark mixture was cooled to ice-bath temperature and partitioned between water (400 mL) and EtOAc (400 mL). The aqueous layer was extracted with EtOAc (2 portions of 150 mL) and the combined organic layers were washed with aqueous 1 M HCl (300 mL), aqueous saturated $NaHCO_3$ (200 mL), aqueous $\frac{1}{2}$ saturated brine (250 mL), dried ($MgSO_4$) and concentrated under vacuum to afford a light-tan solid residue which was purified by flash chromatography (hexane–EtOAc, 1 : 1 (v : v)). The title compound was obtained as a pale yellow solid (9.0 g, 86%). $R_f$ (hexane–EtOAc, 1 : 1 (v : v)) 0.55; mp 79–82 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 8.39 (d, $J = 2.0$ Hz, 1H), 7.76 (dd, $J = 8.2$, 2.0 Hz, 1H), 7.71 (d, $J = 8.2$ Hz, 1H), 2.57 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 196.0, 140.3, 137.1, 135.7, 133.1, 129.1, 101.9, 26.8; LRMS (EI) $m/z = 324$ $[M]^+$; Anal. Calcd. for $C_8H_6BrIO$: C, 29.57; H, 1.86. Found: C, 29.18; H, 2.01.

**(*E*)-Ethyl 3-(4-bromo-3-iodophenyl)but-2-enoate (10).** To an ice-cold suspension of NaH (766 mg, 31.9 mmol, 1.3 eq.) in THF (45 mL) was added dropwise , over 15 min, a solution of triethylphosphonoacetate (7.16 g, 31.9 mmol, 1.3 eq.) in THF (5 mL) during which gas evolution was observed. The resulting pale yellow solution was stirred at ice bath temperature for 15 min and at room temperature for a further 15 min, after which a solution of 4-bromo-3-iodoacetophenone **9** (7.98 g, 24.6 mmol, 1.0 eq.) in THF (35 mL) was added dropwise at room temperature over 10 min. The dark-tan mixture obtained was stirred at room temperature overnight (for convenience), after which it was partitioned between $Et_2O$ (450 mL) and aqueous $\frac{1}{2}$ saturated brine (500 mL). The aqueous layer was extracted with $Et_2O$ (2 portions of 100 mL) and the combined organic phases were washed with brine (200 mL), dried ($MgSO_4$) and the solvent removed under vacuum to afford a dark tan oil. Purification by (repeated) flash chromatography (hexane–$Et_2O$, 3 : 1 (v : v)) delivered pure (*E*)- (6.2 g, 64% as a white solid) and (*Z*)-(1.7 g, 17% as a yellow oil) isomers. Combined yield: 81%. For (*E*)-ethyl 3-(4-bromo-3-iodophenyl)but-2-enoate **10**: $R_f$ (hexane–$Et_2O$, 3 : 1 (v : v)) 0.51; mp 39–42 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.93 (d, $J = 2.2$ Hz, 1H), 7.59 (d, $J = 8.3$ Hz, 1H), 7.28 (dd, $J = 2.2$, 8.3 Hz, 1H), 6.08 (q, $J = 1.3$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 2.50 (d, $J = 1.3$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 2H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 166.5, 152.8, 142.8, 138.2, 132.8, 130.5, 127.5, 118.6, 101.7, 60.4, 18.0, 14.6; LRMS (EI) $m/z = 394$ $[M]^+$; Anal. Calcd. for $C_{12}H_{12}BrIO_2$: C, 36.49; H, 3.06. Found: C, 36.63; H, 3.15.

**(*E*)-3-(4-Bromo-3-iodophenyl)but-2-en-1-ol (11).** To an ice-cold solution of (*E*)-ethyl 3-(4-bromo-3-iodophenyl)but-2-enoate **10** (5.83 g, 14.8 mmol, 1.0 eq.) in $Et_2O$ (45 mL) was added dropwise, over 20 min, a solution of DIBAL in toluene (1.0 M, 34.5 mL, 2.3 eq.). The solution obtained was allowed to reach room temperature and stirred for a further 2.5 h, after which it was re-cooled to ice bath temperature, diluted with $Et_2O$ (60 mL) and quenched by careful addition of brine (50 mL). After vigorous stirring for 5 min a gel-type biphasic system formed, to which was then carefully added aqueous 4 M HCl (80 mL), and the mixture was stirred at 0 °C for 10 min and then at room temperature until a clear biphasic system was obtained (typically 20 min). The aqueous layer was extracted with $Et_2O$ (2 portions of 40 mL), the combined organic layers were washed with brine (40 mL), dried ($MgSO_4$) and the solvent removed under vacuum to afford a very pale yellow oil. Purification by flash chromatography (hexane–EtOAc, 1 : 1 (v : v)) afforded the title compound as a white solid (5.0 g, 96%). $R_f$ (hexane–EtOAc, 1 : 1 (v : v)) 0.30; mp 62–64 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.81 (d, $J = 2.2$ Hz, 1H), 7.47 (d, $J = 8.4$ Hz, 1H), 7.15 (dd, $J = 2.2$, 8.4 Hz, 1H), 5.88 (tq, $J = 1.4$, 6.6 Hz, 1H), 4.26–4.30 (m, 2H), 1.94–1.95 (m, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 143.6, 137.8, 135.5, 132.5, 128.4, 128.3, 127.1, 101.5, 60.1, 16.1; LRMS (EI) $m/z = 352$ $[M]^+$; Anal. Calcd. for $C_{10}H_{10}BrIO$: C, 34.03; H, 2.86. Found: C, 33.98; H, 2.72.

**((2*S*,3*S*)-3-(4-Bromo-3-iodophenyl)-3-methyloxiran-2-yl)methanol (12).** To a suspension of powdered 4 Å molecular sieves (472 mg) in $CH_2Cl_2$ (47 mL) at −25 °C was added dropwise a solution of L-(+)-diethyl tartrate (124 mg, 0.60 mmol, 7.5 mol%) in $CH_2Cl_2$ (1.5 mL), followed by $Ti(O^iPr)_4$ (117 μL, 0.4 mmol, 5 mol%) and finally a freshly prepared solution of $^t$BuOOH in toluene[25] (4.2 ml, 15.9 mmol, 2.0 eq.) with 5 min intervals between additions. After 1.5 h at −25 °C, a solution of (*E*)-3-(4-bromo-3-iodophenyl)but-2-en-1-ol **11** (2.8 g, 7.93 mmol, 1.0 eq.) in $CH_2Cl_2$ (7 mL) was added dropwise over 20 min and stirring continued for a further 4 h at this temperature. The reaction was quenched at −25 °C by addition of aqueous 10% NaOH in brine (0.73 mL) followed by $Et_2O$ (4.5 mL). After stirring at −25 °C for 5 min, this suspension was allowed to reach 5 °C over 10 min, and then $mgSO_4$ (633 mg) and Celite (84 mg) were simultaneously added. After stirring at room temperature for 10 min, the suspension was filtered through a short pad of Celite, and the filtrate was concentrated under vacuum to afford a turbid pale yellow oil which was then taken up in toluene (2 portions of 150 mL) and concentrated under vacuum. The crude product was obtained as a white solid (2.91 g, quantitative, 92–94% ee), which typically was used without further purification. If desired, it can be re-crystallized from hot hexane–$Et_2O$, 2 : 1 (v : v) (approximately 300 mL) affording the title compound as white needles (2.6 g, 91%, >99% ee). $R_f$ (hexane–EtOAc, 1 : 1 (v : v); double elution) 0.50; mp 59–61 °C; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.75 (d, $J = 2.1$ Hz, 1H), 7.50 (d, $J = 8.3$ Hz, 1H), 7.11 (dd, $J = 2.1$, 8.3 Hz, 1H), 3.88 (dd, $J = 4.4$, 12.2 Hz, 1H), 3.75 (dd, $J = 6.3$, 12.2 Hz, 1H), 2.96 (dd, $J = 4.4$, 6.3, 1H), 1.93 (bs, 1H), 1.59 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 143.1, 137.2, 132.7, 129.0, 126.7, 101.5, 66.1, 61.3, 59.9, 17.7; LRMS (EI) $m/z = 368$ $[M]^+$; $[\alpha]_D^{25}$ −9.2 (*c* 2.2, $CHCl_3$); Anal. Calcd. for $C_{10}H_{10}BrIO_2$: C, 32.55; H, 2.73. Found: C, 32.61; H, 2.67. HPLC retention times ($R_t$): For the (2*S*,3*S*) enantiomer: $R_t$ (OD-H column; hexane–$^i$PrOH, 97 : 3 (v : v); 0.6 mL min$^{-1}$) = 57.7 min.

***rac*-3-(4-Bromo-3-iodophenyl)-3-methyloxiran-2-yl)methanol (12).** To an ice-cold suspension of commercial MCPBA (722 mg, approximately 3.68 mmol of MCPBA, approximately 1.3 eq.) in $CH_2Cl_2$ (6 mL) was added dropwise a solution of (*E*)-3-(4-bromo-3-iodophenyl)but-2-en-1-ol **11** (1.0 g, 2.83 mmol, 1.0 eq.) in $CH_2Cl_2$ (6 mL). The suspension obtained was stirred at ice bath temperature for 15 min and then allowed to reach room temperature, stirred for a further 3.5 h, after which it was re-cooled to −5 °C and filtered through a short pad of Celite. To the pale yellow filtrate obtained was added $Ca(OH)_2$ (80 mg) and this suspension was stirred for 5 min at −5 °C, after which a small portion of $Na_2SO_4$ was added and stirring was continued for a further 5 min at this temperature. After filtration through a short pad of Celite, the solvent was removed under vacuum to afford a viscous yellow oil which, upon standing under high vacuum, crystallized. Purification by short-column chromatography filtration (silica gel; fast elution; hexane–EtOAc, 1 : 1 (v : v) with 2% $NEt_3$) afforded the title compound as a white solid (950 mg, 91%). HPLC retention times ($R_t$): For the (2*R*,3*R*) enantiomer: $R_t$ (OD-H column; hexane–$^i$PrOH, 97 : 3 (v : v); 0.6 mL min$^{-1}$) = 51.7 min. For the (2*S*,3*S*) enantiomer: $R_t$ (OD-H column; hexane–$^i$PrOH, 97 : 3 (v : v); 0.6 mL min$^{-1}$) = 57.7 min.

**(2*R*,3*S*)-3-(4-Bromo-3-iodophenyl)-3-methyloxirane-2-carbaldehyde (13).** A solution of oxalyl chloride (1.78 mL, 20.28 mmol, 2.0 eq.) in $CH_2Cl_2$ (90 mL) was cooled to −78 °C and treated with a solution of DMSO (2.9 mL, 40.8 mmol, 4.0 eq.) in $CH_2Cl_2$ (7 mL) over 15 min, during which period gas evolution was observed. After stirring at this temperature for 15 min, a solution of ((2*S*,3*S*)-3-(4-bromo-3-iodophenyl)-3-methyloxiran-2-yl)methanol **12** (3.76 g, 10.19 mmol, 1.0 eq.) in $CH_2Cl_2$ (25 mL) was added dropwise over a period of 0.5 h, after which a turbid-white mixture was obtained. This mixture was stirred at −78 °C for 0.5 h, after which pre-cooled $Et_3N$ (11.26 mL, 81.52 mmol, 8.0 eq.) was added dropwise over 10 min, and the resulting mixture was then allowed to warm to −30 °C over 1 h. The yellow mixture obtained was poured at this temperature onto hexane (140 mL) and $CH_2Cl_2$ (200 mL) and gently shaken with pH 7 phosphate buffer (80 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (2 portions of 30 mL). The combined organic layers were washed with aqueous 1 M $KHSO_4$ (2 portions of 150 mL), aqueous $\frac{1}{3}$ saturated $NaHCO_3$ (2 portions of 30 mL), brine (150 mL) and dried ($Na_2SO_4$). Removal of the solvent under vacuum afforded a thick yellow oil which was crudely purified *via* a short-column chromatography filtration (silica gel; fast elution; hexane–EtOAc, 1 : 1 (v : v) with 2% $NEt_3$) to afford a thick pale yellow oil that eventually crystallized upon standing in the cold (3.40 g) and was used without further purification. $R_f$ (hexane–EtOAc, 1 : 1 (v : v)) 0.57; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 9.64, (d, $J$ = 4.0 Hz, 1H), 7.96 (d, $J$ = 2.2 Hz, 1H), 7.73 (d, $J$ = 8.3 Hz, 1H), 7.40 (dd, $J$ = 2.2, 8.3 Hz, 1H), 3.48 (d, $J$ = 4.0, 1H), 1.82 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 205.6, 142.2, 137.5, 132.9, 129.2, 127.3, 101.1, 66.2, 62.0, 16.9; LRMS (EI) $m/z$ = 366 [M]$^+$.

**(2*R*,3*S*)-3-(4-bromo-3-iodophenyl)-2-methyl-3-vinyloxirane (14).** To an ice-cold slurry of methyltriphenylphosphonium bromide (4.97 g, 13.90 mmol, 1.5 eq.) in THF (100 mL) was added a solution of KHMDS in toluene (0.5 M, 24.1 mL, 1.3 eq.) over 15 min. The bright-yellow suspension obtained was allowed to reach room temperature and stirred for a further 1.5 h, after which it was re-cooled to 0 °C and a solution of (crudely purified) (2*R*,3*S*)-3-(4-bromo-3-iodophenyl)-3-methyloxirane-2-carbaldehyde **13** (3.33 g, 9.1 mmol, 1.0 eq.) in THF (17 mL) was then added dropwise over a 10 min period. The tan suspension obtained was allowed to reach room temperature and stirred for a further 1.5 h, after which it was re-cooled to ice bath temperature and filtered through a short Celite pad to afford a deep-red solution. Removal of the solvent under vacuum afforded a tan oil, which was crudely purified by short-column chromatography filtration (silica gel; fast elution; $Et_2O$) to afford a tan oil that was used without further purification (2.97 g). $R_f$ (hexane–$Et_2O$, 3 : 1 (v : v)) 0.60; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.84 (d, $J$ = 2.2 Hz, 1H), 7.57 (d, $J$ = 8.3 Hz, 1H), 7.19 (dd, $J$ = 2.2, 8.3 Hz, 1H), 5.82 (sept, $J$ = 7.0, 10.5, 17.3 Hz, 1H), 5.51 (ddd, $J$ = 0.9, 1.4, 17.3 Hz, 1H), 5.44 (ddd, $J$ = 0.8, 1.4, 10.5 Hz, 1H), 3.24 (d, $J$ = 7.0 Hz, 1H), 1.62 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 143.4, 137.2, 133.8, 132.7, 132.5, 126.7, 121.7, 121.7, 101.5, 67.0, 61.3, 17.5; LRMS (EI) $m/z$ =364 [M]$^+$.

**(*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-enal (15).** To a −78 °C cooled solution of (crudely purified) (2*R*,3*S*)-3(4-bromo-3-iodophenyl)-2-methyl-3-vinyloxirane **14** (2.81 g, 7.70 mmol, 1.0 eq.) in $CH_2Cl_2$ (110 mL) was added $BF_3{\cdot}Et_2O$ (1.1 mL, 8.68 mmol, 1.12 eq.) and the resulting deep-pinkish solution was stirred at this temperature for 10 min, after which it was poured onto $Et_2O$ (300 mL) and aqueous $\frac{1}{3}$ saturated $NaHCO_3$ (200 mL). The layers were separated and the aqueous phase was extracted with $Et_2O$ (2 portions of 60 mL). The combined $Et_2O$ extracts were washed with brine (100 mL), dried ($Na_2SO_4$) and concentrated to a golden oil, which was then purified by flash chromatography (hexane–$Et_2O$, 3 : 1 (v : v)) to afford the title compound as a pale yellow oil (1.9 g, 52% based on allylic alcohol **12**) that was either best kept frozen in a benzene matrix under argon or used immediately. $R_f$ (hexane–$Et_2O$, 3 : 1 (v : v)) 0.47; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 9.52, (s, 1H), 7.71 (d, $J$ = 2.2 Hz, 1H), 7.60 (d, $J$ = 8.3 Hz, 1H), 7.07 (ddd, $J$ = 0.4, 2.2, 8.3, Hz, 1H), 6.12 (ddd, $J$ = 0.40, 10.7, 17.6 Hz, 1H), 5.46 (d, $J$ = 10.7, 1H), 5.20 (d, $J$ = 17.6, 1H), 1.51 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 198.5 141.1, 139.5, 137.4, 133.1, 129.2, 129.0, 118.7, 102.2, 57.4, 20.4; LRMS (EI) $m/z$ = 337 [M − $C_2H_3$]$^+$; $[\alpha]_D^{25}$ +27.8 (*c* 1.3, $CHCl_3$).

**(*R*)-2-(4-Bromo-3-iodophenyl)-2-methylbut-3-en-1-ol (16).** A solution of (*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-enal **15** (1.18 g, 3.23 mmol, 1.0 eq.) in MeOH (35 mL) at 0 °C was treated with $NaBH_4$ (114 mg, 3.0 mmol, 0.9 eq.). After stirring for 15 min at ice bath temperature, the solution was allowed to warm to room temperature and stirred for a further 2 h, at which time it was concentrated to half of its initial volume and partitioned between water (15 mL) and $Et_2O$ (50 mL). The aqueous layer was extracted with $Et_2O$ (20 mL) and EtOAc (20 mL) and the combined organic phases were washed with brine (10 mL), dried ($NaSO_4$) and concentrated under vacuum to afford a yellow oil residue which typically was used without further purification. For analytical purposes the crude product was purified by flash chromatography on silica gel (hexane–EtOAc, 1 : 1 (v : v)) (960 mg, 81%). $R_f$ (hexane–EtOAc, 1 : 1 (v : v)) 0.52; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.81 (d, $J$ = 2.3 Hz, 1H), 7.55 (d, $J$ = 8.4 Hz, 1H), 7.20 (dd, $J$ = 2.3, 8.4 Hz, 1H), 5.98 (dd, $J$ = 10.8, 17.6 Hz, 1H), 5.30 (dd, $J$ = 0.9, 10.8, 2H), 5.14 (dd, $J$ = 0.9, 17.6, 1H), 3.74 (s, 2H), 1.38 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 145.9, 142.6,

139.3, 132.6, 128.7, 127.9, 115.9, 101.7, 69.7, 46.8, 22.9; LRMS (EI) $m/z = 368$ $[M]^+$.

**Determination of the ee of alcohol (16) using the Alexakis reagent.** To the Alexakis reagent[18] (0.10 mL of a 0.2 M solution in benzene, 0.02 mmol, 1.1 eq.) was added a solution of (*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-en-1-ol **16** (7.0 mg, 0.018 mmol, 1.0 eq.) in benzene (0.2 mL) and the resulting solution was left stirring at room temperature under argon for 15 h. The resulting solution was then transferred into an NMR tube and approximately 100 μL of $C_6D_6$ were added for locking. For *rac*-**17**: $^{31}$P-NMR ($C_6D_6$, 202 MHz) $\delta$ 139.0 and 138.8 (equal intensities). For **17**: $^{31}$P-NMR ($C_6D_6$, 202 MHz) $\delta$ 138.8.

**(*R*)-(2-(4-Bromo-3-iodophenyl)-2-methylbut-3-enyloxy)(*tert*-butyl)dimethylsilane (22).** To a solution of TBDMSCl (131 mg, 0.89 mmol, 1.3 eq.) and imidazole (122 mg, 1.77 mmol, 2.6 eq.) in DMF (0.65 mL) was added a solution of (crude) (*R*)-2-(4-bromo-3-iodophenyl)-2-methylbut-3-en-1-ol **16** (245 mg, 0.66 mmol, 1.0 eq.) in DMF (1.35 mL) at room temperature. After stirring at this temperature for 7 h, the resulting solution was partitioned between aqueous 1 M HCl (15 mL) and $Et_2O$ (25 mL). The organic layer was washed with a second portion of aqueous 1 M HCl (15 mL) and the combined acidic layers were extracted with $Et_2O$ (10 mL). The combined organic layers were washed with aqueous $\frac{1}{2}$ saturated $NaHCO_3$ (25 mL), brine (15 mL), dried ($Na_2SO_4$) and concentrated under vacuum to afford a pale yellow residue. Purification by flash chromatography on silica gel (hexane–$Et_2O$, 3 : 1 (v : v)) delivered the title compound as a clear oil (254 mg, 80% based on **15**). $R_f$ (hexane–$Et_2O$ 3 : 1 (v : v)) 0.69; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 7.89 (d, $J = 2.2$ Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 1H), 7.23 (dd, $J = 2.2$, 8.4 Hz, 1H), 6.04 (dd, $J = 10.9$, 17.6 Hz, 1H), 5.21 (dd, $J = 1.2$, 10.9 Hz, 1H), 5.10 (dd, $J = 1.2$, 17.6 Hz, 1H), 3.70 (s, 2H), 1.37 (s, 3H), 0.88 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 152.3, 148.8, 145.1, 137.5, 134.5, 132.5, 119.7, 106.3, 75.7, 51.9, 31.4, 28.2, 23.8, 0.0; LRMS (EI) $m/z = 482$ $[M]^+$; $[\alpha]_D^{25}$ −10.9 (*c* 2.3, $CHCl_3$).

**(*R*)-2-Bromo-5-(2-((*tert*-butyldimethylsilyloxy)methyl)but-3-en-2-yl)benzaldehyde (23).** To a −105 °C to −100 °C cooled slurry of (*R*)-(2-(4-bromo-3-iodophenyl)-2-methylbut-3-enyloxy)(*tert*-butyl)dimethylsilane **22** (429 mg, 0.89 mmol, 1.0 eq.) in toluene (14.8 mL) was added a solution of $^n$BuLi in hexanes (1.6 M, 1.02 mmol, 0.64 mL, 1.15 eq.) over approximately 8 s. After stirring at this temperature for 2 min, DMF (193 μL, 2.49 mmol, 2.8 eq.) was added over 5 s. The resulting pale yellow solution was stirred at −103 °C to −95 °C for 1.5 h and then allowed to reach −40 °C over 0.5 h, after which the cooling bath was replaced by a water bath and stirring was continued for a further 10 min. The resulting pale yellow solution was then partitioned between $Et_2O$ (80 mL) and water (15 mL) and the aqueous layer was extracted with $Et_2O$ (2 portions of 20 mL). The combined organic layers were washed with $\frac{1}{2}$ brine (20 mL), dried ($Na_2SO_4$) and concentrated under vacuum affording a pale yellow oil residue. Purification by flash chromatography on silica gel (hexane, hexane–$Et_2O$, 6 : 1 (v : v)) delivered the title compound as a colorless oil (242 mg, 71%). $R_f$ (1st elution, hexane–$Et_2O$, 6 : 1 (v : v); 2nd elution, hexane) 0.71; $^1$H-NMR (d-acetone, 300 MHz) $\delta$ 10.34 (s, 1H), 7.95 (d, $J = 2.5$ Hz, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.65 (dd, $J = 2.5$, 8.4 Hz, 1H), 6.16 (dd, $J = 10.9$, 17.6 Hz, 1H), 5.23 (dd, $J = 1.2$, 10.9 Hz, 1H), 5.17 (dd, $J = 1.2$, 17.6 Hz, 1H), 3.86 (d, $J = 0.8$ Hz, 2H), 1.45 (s, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 191.3, 146.5, 143.6, 135.3, 133.6, 133.1, 129.0, 124.0, 113.9, 70.2, 46.8, 25.5, 22.2, 18.0, −6.2; LRMS (EI) $m/z = 384$ $[M]^+$.

**(*R*,*Z*)-Ethyl-2-azido-3-(2-bromo-5-(2-((*tert*-butyldimethylsilyloxy)methyl)but-3-en-2-yl)phenyl)acrylate (24).** Sodium metal (35.9 mg, 1.56 mmol, 6.0 eq.) was dissolved in EtOH (1.0 mL). To the resulting solution was slowly added, at −15 °C and over 1 h, a solution of (*R*)-2-bromo-5-(2-((*tert*-butyldimethylsilyloxy)methyl)but-3-en-2-yl)benzaldehyde **23** (100 mg, 0.26 mmol, 1.0 eq.) and ethyl azidoacetate (0.71 mL of a 2.39 M solution in EtOH, 1.69 mmol, 6.5 eq.). During addition a milky pale yellowish suspension formed. The temperature was then allowed to rise from −15 °C to −10 °C and stirring was continued for a further 18 h. The orange suspension obtained was then stirred at room temperature for 0.5 h, re-cooled to ice bath temperature, quenched with aqueous saturated $NH_4Cl$ (0.7 mL) and gently partitioned between $Et_2O$–EtOAc (1 : 1 (v : v)) (30 mL) and aqueous $\frac{1}{2}$ saturated $NH_4Cl$ (10 mL). The deep-tan aqueous layer was further extracted with $Et_2O$–EtOAc (1 : 1 (v : v)) (3 portions of 10 mL); the combined organic layers were washed with aqueous $\frac{1}{2}$ saturated brine (10 mL) and dried ($Na_2SO_4$). The obtained tan solution was then concentrated to approximately 5 mL and filtered through a short column of silica gel ($Et_2O$). After removal of the solvent under vacuum, a reddish oil was obtained which was purified by PTLC (hexane–$Et_2O$, 3 : 1 (v : v)). The title compound was obtained as a colourless oil (78 mg, 60%). $R_f$ (1st elution, hexane–$Et_2O$, 3 : 1 (v : v); 2$^{nd}$ elution, pentane) 0.63 (note: the $R_f$ values for the starting material and the product are very similar); $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 8.14 (d, $J = 2.4$ Hz, 1H), 7.55 (d, $J = 8.5$ Hz, 1H), 7.30 (d, $J = 2.6$ Hz, 1H), 7.23 (dd, $J = 2.6$, 8.5 Hz, 1H), 6.11 (dd, $J = 10.9$, 17.6 Hz, 1H), 5.23 (dd, $J = 1.2$, 10.9 Hz, 1H), 5.13 (dd, $J = 1.2$, 17.6 Hz, 1H), 4.43 (q, $J = 7.1$ Hz, 2H), 3.77 (d, $J = 1.6$ Hz, 2H), 1.46 (t, $J = 7.1$ Hz, 3H; partial overlap with s at $\delta = 1.43$ ppm), 1.43 (s, 3H; partial overlap with s at $\delta = 1.46$ ppm), 0.88 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 169.0, 150.6, 149.3, 137.8, 137.7, 136.0, 135.4, 132.7, 129.6, 128.3, 119.5, 76.0, 68.1, 52.3, 31.4, 28.2, 23.9, 19.9, 0.0.

**(*R*)-Ethyl-4-bromo-7-(1-*tert*-butyldimethylsilyoxy)-2-methylbut-3-en-2-yl)-1*H*-indole-2-carboxylate (25).** A solution of (*R*,*Z*)-ethyl 2-azido-3-(2-bromo-5-(1-*tert*-butyldimethylsilyoxy)-2-methylbut-3-en-2-yl)phenyl)acrylate **24** (74 mg, 0.14 mmol) in *meta*-xylene (1.3 mL) was added dropwise over 1 h to refluxing *meta*-xylene (3.7 mL). The obtained solution was refluxed for a further 3.5 h, after which the solvent was removed under vacuum to afford a tan oil. Purification by PTLC (hexane–$Et_2O$, 5 : 1 (v : v)) afforded the title compound as a pale yellow oil (45 mg, 69%). $R_f$ (hexane–$Et_2O$, 5 : 1 (v : v)) 0.27; $^1$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 9.87, (brs, 1H), 7.33 (d, $J = 7.9$ Hz, 1H), 7.28 (d, $J = 2.3$ Hz, 1H), 7.18 (d, $J = 7.9$ Hz, 1H), 6.24 (dd, $J = 10.8$, 17.7 Hz, 1H), 5.40 (dd, $J = 1.1$, 10.8 Hz, 1H), 5.31 (dd, $J = 1.1$, 17.7 Hz, 1H), 4.45 (q, $J = 7.1$ Hz, 2H), 4.02 (d, $J = 10.0$ Hz, 1H), 3.87 (d, $J = 10.0$ Hz, 1H), 1.51 (s, 3H), 1.46 (t, $J = 7.1$ Hz), 0.87 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 167.3, 149.3, 141.7, 134.5, 134.0, 133.0, 129.8, 129.0, 120.5, 120.4, 113.9, 76.2,

66.8, 52.3, 31.6, 28,8, 24.1, 20.1, 0.0; LRMS (EI) $m/z = 465$ $[M]^+$; $[\alpha]_D^{25}$ +22.7 (*c* 2.15 in $CHCl_3$).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# An Intramolecular Heck Reaction that Prefers a 5-*endo*- to a 6-*exo*-*trig* Cyclization Pathway

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**Abstract:** A regioselective aromatic Claisen rearrangement was used to prepare **17a**, the precursor of triflate **17e**. The intramolecular Heck reaction of **17e** is promoted only by bidentate phosphine ligands, giving exclusively and in excellent yield **20**, the product of a 5-*endo*-*trig* cyclization, despite the possibility for a 6-*exo*-*trig* pathway.

**Key words:** intramolecular Heck reaction, 5-*endo*-*trig* cyclization, regioselective Claisen rearrangement

'Teleocidin B', first isolated in 1960 by Takashima and Sakai from the mycelia of *Streptomyces mediocidicus*,[1] is comprised of four diastereomeric compounds, teleocidins B-1 to B-4 (**1a**–**d**).[2] The teleocidins B are related to other natural products, namely lyngbyatoxin A (**2a**; aka teleocidin A-1) and (–)-indolactam V (**2b**), but are structurally more complex in that they possess two quaternary carbon centers embedded within a 6-membered cyclic framework bridging the 6- and 7-positions of the indole nucleus (Figure 1).[3,4]

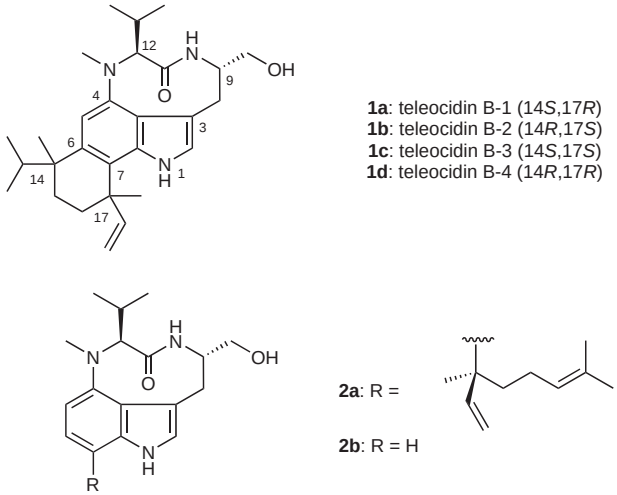
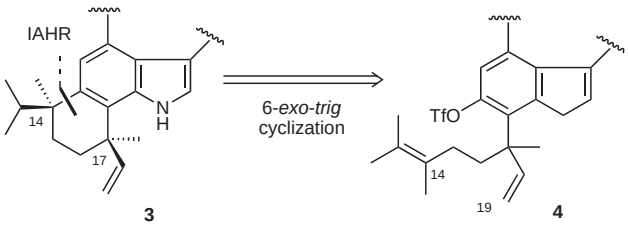



**Figure 1** Structures of teleocidins B (**1a**–**d**), lyngbyatoxin A (**2a**) and indolactam V (**2b**).

'Teleocidin B' has a strong irritating and vesicatory action on human skin[1] and is also a potent tumor promoter.[2a] Like the other indolactam alkaloids, the teleocidins B exert their biological activity by mimicking 1,2-diacylglycerols in the activation of protein kinase C (PKC).[5a] Since activation of PKC is a crucial step in the regulation of several essential cellular processes, the teleocidins B constitute a leading target in pharmaceutical research.[5]

As part of ongoing studies towards the total synthesis of the teleocidins B, we envisioned that the quaternary carbon center at C14 could be stereoselectively installed via an intramolecular asymmetric Heck reaction (IAHR; Scheme 1).[6] In this reaction, best results are usually obtained with conditions that promote the formation of cationic intermediates, where the chiral ligand is believed to remain fully chelated therefore maximizing the possibility for asymmetric induction. Typically, this is accomplished by combining a bidentate chiral ligand with triflates as electrophiles.[6–8] With respect to the regioselectivity in the cyclization step (**4** to **3**), we expected that, in accordance with the Baldwin rules[9a,b] and in line with what is usually observed in metal-catalyzed cross-coupling reactions,[9c,d] the desired 6-*exo*-*trig* cyclization to C14 would be favored over the alternative 5-*end*-*trig* to C19.




**Scheme 1** Key step for formation of the carbocyclic framework of the teleocidins B.

To test the feasibility of this approach we started by investigating how the severe steric bulk, derived from the neighboring quaternary carbon center at C17, would affect the formation of the six-membered carbocycle skeleton. To this end, we turned our attention to a simplified model target, indole **5**. A simplified retrosynthetic analysis of **5** is shown in Scheme 2. As before, the carbocyclic moiety in indole **5** was envisioned to be formed via an intramolecular Heck reaction (IHR) of **6** (as the corresponding triflate).[6] Indole **6** can be prepared by an aromatic Claisen rearrangement of **7**,[10,11] which in turn could be obtained via a Hemetsberger–Knittel reaction[12] of the corresponding azidocinnamate (not shown) prepared from ethyl azidoacetate (**8**), 4-hydroxybenzaldehyde (**9**) and geranyl bromide (**10**).[10]

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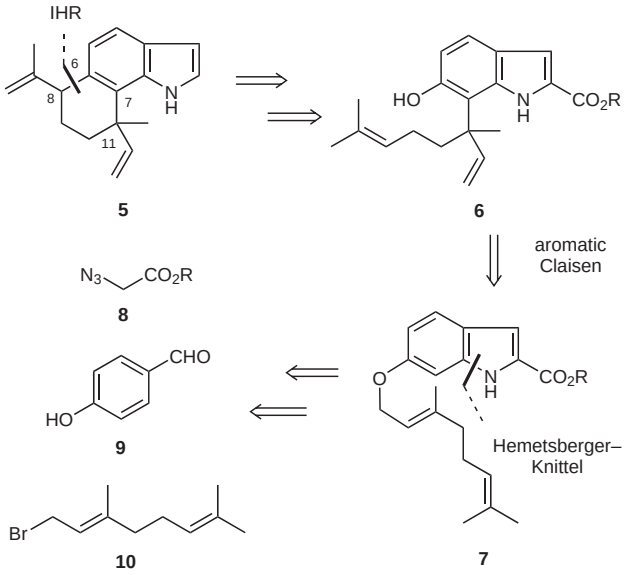
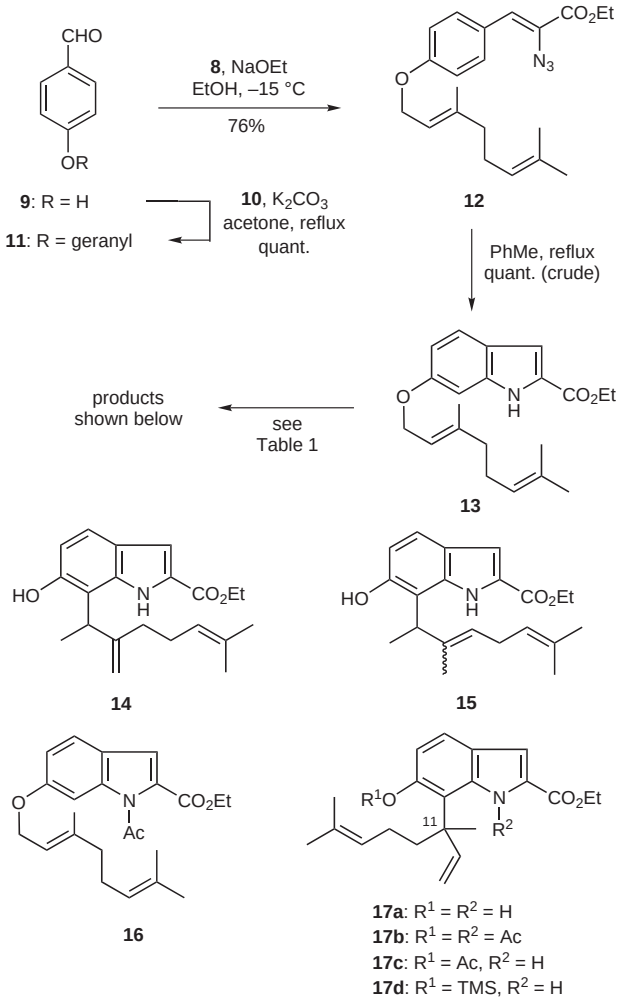



**Scheme 2** Retrosynthetic analysis for model indole **5**.

Following a literature procedure, etherification of 4-hydroxybenzaldehyde (**9**) with geranyl bromide (**10**) and $K_2CO_3$ was accomplished in refluxing acetone in quantitative yield (Scheme 3).[13] Subsequent NaOEt-promoted condensation of **11** with ethyl azidoacetate (**8**) at low temperature afforded azide **12** in good yield. Thermolysis of **12** in refluxing toluene gave the known indole **13** in excellent yield and high purity.[10]

When this substrate was subjected to the usual conditions for the aromatic Claisen rearrangement (refluxing in dimethylaniline, entry 1, Table 1), only an equimolar inseparable mixture of **14** and **15** was obtained, presumably formed through further rearrangements of the expected indole **17a**. These so-called abnormal aromatic Claisen rearrangements[14] can in principle be avoided by trapping the phenolic oxygen in **17a**. Traditionally this has been accomplished by in situ conversion to the corresponding acetate.[15a,b] Using the conditions developed by Kishi (NaOAc in refluxing $Ac_2O$),[15a] we hoped to obtain the rearranged indole as the corresponding *N*,*O*-diacetate **17b**. The desired rearranged product was indeed produced, but as the *O*-acetate **17c** and only in poor yield. The main product was instead the N-acylated compound **16** (entry 2). Performing the reaction in a refluxing mixture of $Ac_2O$ and dimethylaniline inverted the previous ratio, delivering the known **17c** as the main product together with a small amount of the N-acylated by-product **16** (entry 3).[10] The highest selectivity for the desired product was obtained using the conditions developed by Fukuyama, reflux in a mixture of HMDS and dimethylaniline,[15c] thus trapping **17a** as the corresponding TMS ether **17d**. Subsequent in situ acidic hydrolysis yielded **17a** (entry 4) in 88% over the two steps.[16]

As previously noticed by others, notably Moody and coworkers, the Claisen rearrangement is completely regioselective for the 7-position of the indole nucleus.[10,17] We have calculated the relative energies for **18** and **19**



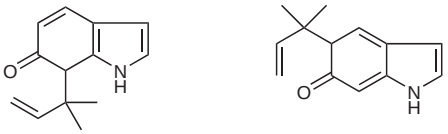

**Scheme 3** Preparation and product distribution in the Claisen rearrangement of indole **13** (see Table 1).

**Table 1** Conditions Investigated for the Aromatic Claisen Rearrangement of Indole **13**

| Entry | Reaction conditions[a] | Product distribution[b] |
|---|---|---|
| 1 | Dimethylaniline | 55% of **14** and **15** (1:1 inseparable mixture) |
| 2 | NaOAc (1.5 equiv) in $Ac_2O$, 170 °C | 45% of **16**<br>33% of **17c**<br>5% of **13** |
| 3 | $Ac_2O$ in dimethylaniline (1:1, v/v) | <5% of **16**<br>61% of **17c** |
| 4[c] | i) HMDS (10 equiv) in dimethylaniline<br>ii) aq HCl–EtOH (0 °C) | 88% of **17a** |

[a] Unless stated otherwise, all reactions were performed at 195 °C in a closed vessel.
[b] Isolated yields.
[c] See ref. 16 for experimental details.

(Figure 2), simplified versions of the two possible intermediates in the Claisen rearrangement at C7 and C5, respectively. In accordance with the Bell–Evans–Polanyi principle[18] the relative energies of high-energy intermediates should correlate well with the relative barriers for the two possible rearrangements. We found a difference of 40 kJ $mol^{-1}$ in favor of **18**, in good agreement with the observed selectivity.[19] The reason for the high energy difference between superficially similar intermediates is that only **18** preserves an aromatic pyrrole moiety in its structure.



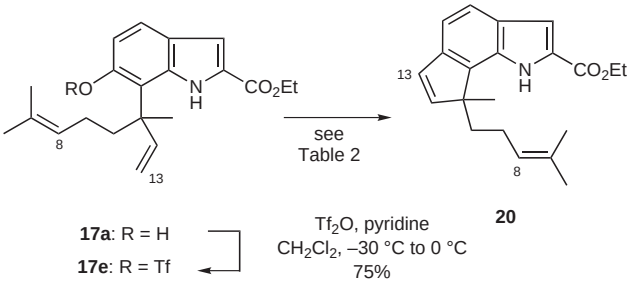
**18** **19**

**Figure 2** Simplified versions of the two possible intermediates in the Claisen rearrangement.

Having installed the C11 quaternary carbon we proceeded by converting **17a** into the corresponding triflate **17e**. This was accomplished in good yield by treating **17a** with $Tf_2O$ in the presence of pyridine at low temperature (Scheme 4).

For the cyclization of **17e** we started by investigating the use of *rac*-BINAP (entry 1, Table 2). To our surprise, the product was not the expected cyclohexadieno-indole **5**. Instead, NMR analysis indicated the cyclopentadieno-indole **20**, presumably obtained via what is normally considered to be a disfavored 5-*endo*-*trig* cyclization mode. Whereas 5-*endo*-type products in IHR are not unprecedented they are rare, being confined to special substrates such as *N*-vinyl-2-haloarylamines[20], aryl/alkenyl halides containing an appropriate α,β-unsaturated carbonyl group[21] or 1,1-difluoro-1-alkenes.[22] Furthermore, their formation can frequently be rationalized by alternative mechanisms other than a direct 5-*endo* cyclization.[23] Additionally, when this cyclization mode operates, it typically requires harsher conditions and often produces only low yields of the products,[24] whereas in our case indole **20** was obtained in high yield and the reaction was complete in about 3.5 h.

In order to obtain a better understanding of this process, and in particular if the regioselectivity of the cyclization could be reversed into the desired 6-*exo* mode, we screened several readily available ligands (Table 2). We started by investigating the use of the classic $PPh_3$ [with and without LiCl as additive, entries 2 and 3, respectively, and in the form of $Pd(PPh_3)_4$, entry 4], $AsPh_3$ (entry 5) and then moved on to bulkier ligands such as P(*t*-Bu)$_3$ (entry 6) and biphenyl dicyclohexyl phosphine (entry 7). However, all of these monodentate ligands failed to deliver product and only starting material was recovered. This suggests that for this system, and in line with the generally accepted mechanism for the cationic pathway in the Heck




**Scheme 4** Formation of cyclopentadieno-indole (**20**) via a 5-*endo*-*trig* intramolecular Heck reaction.

**Table 2** Ligands Screened for the IHR of Indole **17e**

| Entry | Conditions[a,b] | Results[c] |
|---|---|---|
| 1 | $Pd(OAc)_2$, *rac*-Binap, 3.5 h | 88% of **20** |
| 2 | $Pd(OAc)_2$, $PPh_3$, TEA, 28 h | – |
| 3 | $Pd(OAc)_2$, $PPh_3$, LiCl, TEA, 28 h | – |
| 4 | $Pd(PPh_3)_4$, LiCl, $Et_3N$, 28 h | – |
| 5 | $Pd_2(dba)_3$, $AsPh_3$, 30 h | Traces of **20**[d] |
| 6 | $Pd(OAc)_2$, P(*t*-Bu)$_3$, 30 h | Traces of **20**[d] |
| 7 | $Pd(OAc)_2$, biphenyl dicyclohexyl phosphine, 43 h | Traces of **20**[d] |
| 8 | $Pd(OAc)_2$, dppf, 3.5 h | 88% of **20** |
| 9 | $Pd(OAc)_2$, dppb, 3.5 h | 85% of **20** |
| 10 | $Pd(OAc)_2$, dppp, 2.5 h | 88% of **20** |
| 11 | $Pd(OAc)_2$, dppe, 2.5 h | 94% of **20** |
| 12 | $Pd(OAc)_2$, dppbz, 24 h | **20**:**17e**[e] 2.6:1 |
| 13 | $Pd(OAc)_2$, triphos, 24 h | **20**:**17e**[e] 1:1.8 |

[a] All reactions were performed in refluxing THF and unless stated otherwise, $K_2CO_3$ was used as the base.
[b] For experimental details, see ref.[25,]
[c] Isolated yields; '–' stands for only starting material **17e** recovered.
[d] As judged by TLC.
[e] Ratio based on crude $^1H$ NMR.

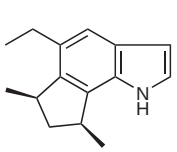
reaction, a bidentate ligand is required for the stability of the active catalyst.

Hence we subsequently investigated bidentate ligands other than *rac*-BINAP. In contrast to the monodentate ligands, all the bidentate phosphines screened succeeded in promoting the cyclization reaction, but again only the 5-*endo* product **20** was obtained (entries 8–13). The incomplete conversion, even after long reaction times, observed when dppbz and triphos were used (entries 12 and 13, respectively) together with the fact that a slightly faster reaction was observed for dppe and dppp (entries 10

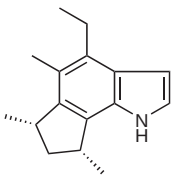
and 11, respectively) suggests that ideally the ligand bite angle should be slightly less than 90°.

To the best of our knowledge, this is the first example where, having available the possibility for a 6-*exo*-*trig* path, the IHR occurs exclusively to afford high yields (up to 94%) of the 5-*endo*-*trig* cyclized product. This result is likely to be a consequence of two factors: i) the steric bulk of the neighboring quaternary carbon, which positions and eventually locks the C12–C13 double bond of **17e** in the proximity of the oxidatively added Pd; and ii) in the migratory insertion step, occurring in the coordination sphere of Pd, the bond formation is initiated at a long C–C distance, and can thus occur in geometries that are distinctly different from those allowed in systems for which the Baldwin rules were originally developed.[9a,b]

Finally, it is noted that this serendipitous finding could potentially be used as an entry to natural products such as the trekentrins [e.g., *cis*-trekentrin A (**21**)][26] and the herbindoles [e.g., herbindole B (**22**)][27] (Figure 3), taking full advantage of the regioselective Claisen rearrangement–5-*endo*-*trig* Heck cyclization sequence.



*cis*-trikentrin A (**21**)



herbindole B (**22**)

**Figure 3** Examples of natural products containing a 6,7-cyclopentena-indole core.

## Acknowledgment

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(16) **Procedure for the Preparation of 17a.**
A solution of indole **13** (1.42 g, 4.16 mmol, 1.0 equiv), HMDS (8.7 mL, 41.8 mmol, 10 equiv) and dimethylaniline (30 mL) in a closed, thick-wall glass container was inserted in a salt bath (53% $KNO_3$, 40% $NaNO_2$ and 7% $NaNO_3$, by weight) at 195 °C until TLC showed no more starting material (aprox. 6–7 h). After reaching r.t., the reaction mixture was partitioned between $Et_2O$ (150 mL) and 3 M aq HCl (150 mL); the organic layer was further washed with 3 M aq HCl (100 mL), aq $NaHCO_3$ (two portions of 120 mL), brine (50 mL) and dried ($Na_2SO_4$). The solvent was removed under reduced pressure to afford a tan-colored oil, which was dissolved in EtOH (20 mL). The resulting solution was cooled to ice-bath temperature and treated with 3 M aq HCl (2.5 mL). After approx. 10 min, the reaction

mixture was diluted with $Et_2O$ (90 mL), washed with aq $NaHCO_3$ (two portions of 40 mL), brine (20 mL) and dried ($Na_2SO_4$). The resulting solution was concentrated under vacuum to approx. 1/5 of its original volume and eluted/filtered through a short column of silica gel using hexane–$Et_2O$ (2:1). Rearranged indole **17a** (1.25 g, 88%) was obtained as a thick, light-tan-colored oil. $^1$H NMR (300 MHz, $CDCl_3$): δ = 9.38 (br s, 1 H), 7.41 (d, *J* = 8.5 Hz, 1 H), 7.11 (d, *J* = 2.1 Hz, 1 H), 6.67 (d, *J* = 8.5 Hz, 1 H), 6.57 (dd, *J* = 17.8, 10.8 Hz, 1 H), 5.63 (s, 1 H), 5.43 (d, *J* = 17.8 Hz, 1 H), 5.41 (d, *J* = 10.8 Hz, 1 H), 5.07 (m, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 2.18–1.76 (m, 4 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.44 (s, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 162.2, 153.0, 148.7, 137.3, 131.9, 126.1, 124.5, 123.8, 122.1, 114.5, 113.3, 113.1, 108.7, 61.0, 45.5, 39.9, 25.9, 25.6, 24.0, 17.4, 14.7.

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(25) **Typical Procedure for the Preparation of 20.**
A mixture of indole **17e** (50 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.5 mg, 0.01 mmol, 10 mol%), $K_2CO_3$ (44 mg, 0.3 mmol, 3.0 equiv), and the ligand (0.03 mmol, 30 mol%) in degassed THF (2.1 mL) was refluxed for the time shown in Table 2. After cooling to r.t., $H_2O$ (2 mL) was added and the mixture was partitioned between $Et_2O$ (15 mL) and $H_2O$ (10 mL). The organic layer was washed with brine (5 mL), dried ($MgSO_4$) and concentrated under vacuum. The obtained residue was purified by flash chromatography (hexane–ether, 2:1) to afford cyclopentadieno-indole **20** as a faint yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): δ = 8.63 (br s, 1 H), 7.58 (dd, *J* = 0.75, 8.1 Hz, 1 H), 7.29 (d, *J* = 2.0 Hz, 1 H), 7.19 (d, *J* = 8.1 Hz, 1 H), 6.78 (d, *J* = 5.4 Hz, 1 H), 6.39 (d, *J* = 5.4 Hz, 1 H), 4.94 (m, 1 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 2.10–1.59 (m, 4 H), 1.55 (br s, 3 H), 1.44 (s, 3 H), 1.43 (t, *J* = 7.1 Hz, 3 H), 1.36 (br s, 3 H).). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 162.5, 144.7, 141.4, 134.1, 132.7, 131.9, 130.1, 127.6, 126.7, 124.4, 121.4, 116.1, 109.9, 61.2, 54.1, 38.0, 25.8, 23.9, 22.8, 17.7, 14.7.

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# A $C_2$-symmetric nickel diamine complex as an asymmetric catalyst for enecarbamate additions to butane-2,3-dione†

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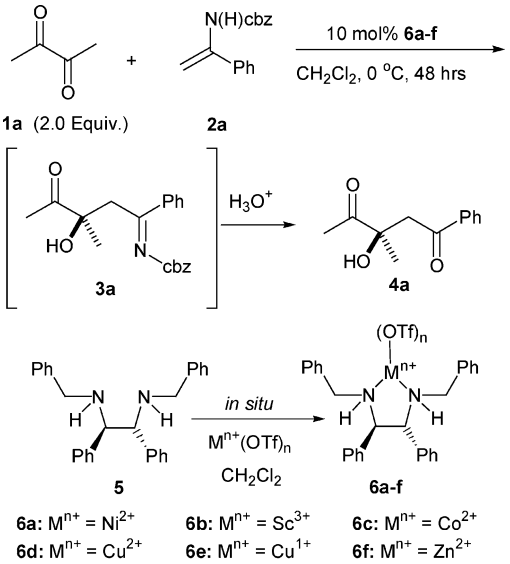
**Butane-2,3-dione was activated towards nucleophilic addition of enecarbamates by a series of metal triflate complexes of a $C_2$-symmetric diamine to give stereogenic, aldol-like, *t*-alcohols, a novel nickel(II) triflate complex was identified as a good catalyst for this asymmetric transformation, and an *aquo* nickel(II) complex was identified by XRD techniques.**

Our group has previously demonstrated the utility of enecarbamates as nucleophiles for C–C bond formation in asymmetric copper catalysed reactions of aldimines and aldehydes that afford stereogenic secondary 1,3-imino alcohols and amines.[1] Although enecarbamates provide a range of potential synthetic utilities, their use as nucleophiles in asymmetric catalysis has only recently been reported.[1]

Herein, we report that simple diketones **1a** and **1b** can be activated towards nucleophilic addition of enecarbamates **2a–c** with a reasonable degree of stereocontrol by a novel Lewis acidic cationic Ni(II) diamine complex, providing access to otherwise synthetically demanding stereogenic tertiary alcohols **4a–e**.[2] A crystal structure of a stable Ni(II) bis-aquo complex of ligand **5** revealed an octahedral geometry at the nickel.[3]

We initially chose to investigate cationic transition metal triflate complexes **6a–f** of a $C_2$-symmetric diamine **5**, prepared *in situ* in $CH_2Cl_2$,[4] as catalysts for the addition of **2a** to **1a**, see Scheme 1. Enecarbamate **2a** was previously shown as a useful enecarbamate in work concerned with aldimine or aldehyde substrates.[1]




**Scheme 1** Aldol-like reaction of enecarbamate **2a** with diketone **1a**, and catalyst preparation.

The substrates were added to the catalyst solution, corresponding to *ca.* 0.07 M with respect to **2a**, *i.e.*, concentration with respect to **6** is 0.007 M.[5] The crude reaction mixtures were treated with 3 N $HCl_{aq}$ to give the easier to handle and analyse diketone product **4a**.[6]

Catalyst **6a** resulted in the formation of product **4a** in a promising yield of 67%, the ee of this tertiary alcohol was 76%. Scandium(III) triflate in combination with **5** failed to catalyse the reaction under the conditions employed (Table 1, entry 2), and cobalt(II) triflate gave only a very small amount of the desired product (5% yield) with 45% ee (Table 1, entry 3). Whilst copper(II) triflate gave a slightly better yield than nickel(II) triflate the ee was slightly lower (Table 1, entry 4 *versus* entry 1), and comparison between catalysts derived from copper(II) and copper(I) triflates revealed the 2+ oxidation state to be superior (Table 1, entry 4 *versus* entry 5). That zinc(II) triflate catalyses the reaction (Table 1, entry 6) with similar selectivity to nickel(II) and copper(II) triflates (Table 1, entries 1 & 4 respectively), suggests similar modes of operation.

Since the best ee was obtained with nickel and, as it is relatively under-studied as a Lewis acid with respect to it's first row neighbours, we selected nickel for further elaboration, even though a slightly better yield was obtained with $Cu(OTf)_2$.[7] Previously, our group has reported the use of copper complexes as asymmetric catalysts,[1] we were keen to expand the scope of our study to other Lewis acidic, metal containing, species which also led us to focus our efforts on the understanding and application of a previously unreported nickel(II) triflate diamine complex.

For nickel(II) triflate variation of catalyst loading and reaction temperature did not give any significant improvement in either yield or ee (see Table 2 *versus* Table 1, entry 1), whilst good improvements were observed for extended reaction times, $CH_2Cl_2$ was also shown to be the best solvent of those tried.

Surprisingly an increase in catalyst loading from 10 to 15 mol% resulted in a reduction in yield (67 *versus* 33%, Table 1, entry 1 and Table 2, entry 1, respectively), although ee was unaffected.

Similarly a reduction in catalyst loading lead to a further reduction in yield but a slight improvement in ee (Table 2, entry 5 *versus* Table 1, entry 1 and Table 2, entry 1). The reaction did not proceed at −30 °C even after 72 h (Table 2, entry 3). Although the reaction did proceed a little at −20 °C, albeit in equimolar conversion to catalyst loading (Table 2, entry 7). Toluene proved to be slightly inferior to $CH_2Cl_2$ (Table 2, entry 8). A reduction of catalyst loading to 6 mol% and concentration to 0.006 M gave a reduced ee (41%) along with a dramatically reduced yield (11%)

**Table 1** Transition metal-triflate catalysed reaction of **1a** with **2a**

| Entry | Catalyst | Yield (%) | EE (%) |
|---|---|---|---|
| 1 | **6a** | 67 | 76 |
| 2 | **6b** | — | — |
| 3 | **6c** | 5 | 45 |
| 4 | **6d** | 72 | 71 |
| 5 | **6e**[a] | 14 | 57 |
| 6 | **6f** | 31 | 75 |

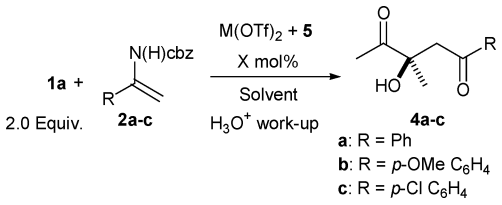
[a] Cu(I)(OTf)·0.5 PhH was used. Yield refers to isolated yield of hydrolysed ketone product.

† Electronic supplementary information (ESI) available: experimental details and analytical data. See http://dx.doi.org/10.1039/b505404d

DOI: 10.1039/b505404d

**Table 2** $Ni(OTf)_2$ + **5** catalysed reactions of **1a** with **2a**–**c**; *Y* = yield of diketone; Tol = toluene; M = Ni(II) unless otherwise stated.




| Entry | Product[a] | Temperature/°C | *X* | Catalyst/mM | Solvent | *Y* (%) | Ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | 0 | 15 | 7 | $CH_2Cl_2$ | 33 | 76 |
| 2 | **4a** [b] | 39 | 10 | 7 | $CH_2Cl_2$ | 27 | 49 |
| 3 | **4a**[c] | −30 | 10 | 7 | $CH_2Cl_2$ | — | — |
| 4 | **4a** | 0 | 6 | 12 | $CH_2Cl_2$ | 20 | 69 |
| 5 | **4a** | 0 | 5 | 7 | $CH_2Cl_2$ | 15 | 79 |
| 6 | **4a** | 0 | 6 | 3 | $CH_2Cl_2$ | 17 | 77 |
| 7 | **4a** | −20 | 6 | 6 | $CH_2Cl_2$ | 6 | 74 |
| 8 | **4a** | 0 | 10 | 8 | Tol | 47 | 75 |
| 9 | **4a** | 0 | 6 | 6 | Tol | 11 | 41 |
| 10 | **4a** | 0 | 10 | 8 | 4 : 1 Tol : $CH_2Cl_2$ | 46 | 80 |
| 11 | **4a** | 0 | 10 | 7 | 1 : 1 Tol : $CH_2Cl_2$ | 32 | 80 |
| 12 | **4a** | 0 | 10 | 9 | 1 : 4 Tol : $CH_2Cl_2$ | 15 | 79 |
| 13 | **4a** | 0 | 10 | 8 | $Et_2O$ | 26 | 70 |
| 14 | **4a** | 0 | 6 | 6 | THF | — | — |
| 15 | **4a** | 0 | 6 | 6 | $CH_3CN$ | 8 | <2 |
| 16 | **4a** [d] | 0 | 10 | 7 | $CH_2Cl_2$ | 94 | 84 |
| 17 | **4b** | 0 | 10 | 7 | $CH_2Cl_2$ | 47 | 45 |
| 18 | **4b** [d] | 0 | 10 | 7 | $CH_2Cl_2$ | 59 | 65 |
| 19 | **4c** | 0 | 10 | 7 | $CH_2Cl_2$ | 20 | 75 |
| 20 | **4c** [d] | 0 | 10 | 7 | $CH_2Cl_2$ | 90 | 82 |
| 21[e] | **4a** | 0 | 10 | 8 | 4 : 1 Tol : $CH_2Cl_2$ | 53 | 48 |
| 22[e] | **4b** | 0 | 10 | 7 | $CH_2Cl_2$ | 84 | 35 |
| 23[e] | **4c** | 0 | 10 | 7 | $CH_2Cl_2$ | 44 | 38 |

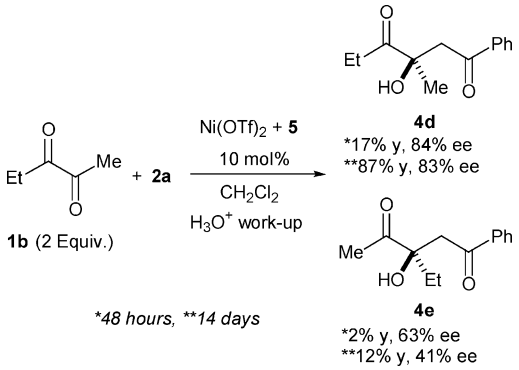
[a] Reaction time was 48 h unless stated otherwise. [b] Black precipitate after 17 h, quenched at 24 h. [c] Reaction time was 72 h, no conversion was observed during the course of the reaction. [d] Reaction time was 336 h. [e] M = Cu(II).

(Table 2, entry 9). Mixtures of toluene and $CH_2Cl_2$ (Table 2, entries 10, 11 & 12) gave higher enantiomeric excesses than use of either solvent alone, but yields were reduced. For comparison **6d** was also used as a catalyst under the same conditions as entry 10 (Table 2, entry 21), as in Table 1 the yield using a copper(II) triflate derived catalyst is slightly higher than that using nickel (53 *versus* 46%) and the ee is somewhat lower (48 *versus* 80%). That concentration (of nickel complex), solvent and temperature can have such a significant influence on yield and ee might be due the formation of dimeric or oligomeric catalyst structures in solution. Dramatic concentration, solvent and temperature effects have been previously reported in other (Lewis acid) nickel catalysed reactions.[8] Trimeric nickel complexes were structurally confirmed for related nickel tmeda complexes in the solid state by Handley *et al.* who note the solution equilibrium between monomeric and trimeric diamine chelated complexes of nickel halides.[9]

The reaction to form **3a** was repeated as per Table 1, entry 1 and monitored with time by $^1$H NMR spectroscopy. We observed that over the first 48 h the reaction seemed to be, approximately, *pseudo* first order with respect to the enecarbamate concentration. The observed initial rate constant ($k_{obsd}$) was calculated from the data obtained over the first 40 h to be $3 \times 10^{-6}$ $s^{-1}$ which implies a reaction half-life of 64.2 h.[10] This reaction was continued for five half lives with aliquots taken at various times (see the electronic supplementary information). At 74% conversion (by $^1$H NMR) the remaining reaction mixture was purified, which gave **4a** in 83% ee. Repetition of this 14 d reaction gave **4a** in 94% yield and 84% ee (Table 2, entry 16). Enecarbamates **2b** and **2c** where also subjected to the same reaction conditions (Table 2, entries 17–20), a marked improvement in yield and ee was observed by extending the reaction time from 48 to over 300 h. The results obtained after 48 h for the nickel catalysed formation of **4b** and **4c** (Table 2 entries 17 and 19 respectively) can be compared with those using copper(II) (Table 2, entries 22 and 23) under the same conditions. For the comparisons given here copper(II) triflate derived catalyst **6d** was found to consistently give lower enantiomeric excesses than the corresponding nickel(II) triflate catalyst, yet under the same conditions higher yields are obtained with the copper catalyst, the largest difference in yield (37%) was observed for the formation of **4b**. Obviously 14 d reactions are not practical in an everyday sense but these results show two principle important points: (i) **6a** is indeed a useful Lewis acid catalyst for activation of diketones to reaction with enecarbamates, and (ii) reactions are only limited by turnover frequency and not catalyst inhibition or decomposition.[11] A related study by Evans *et al.* concerning copper catalysed enolsilane addition to pyruvate esters revealed that addition of TMSOTf greatly enhanced reaction rate (catalyst turnover), by assisting the intermolecular silylation of the respective product.[12] In our case the addition of TMSOTf to the reaction of **1a** with **2a** might affect an intermolecular silylation giving the corresponding TMS-ether of **3a**. Under the same conditions as those for Table 1, entry 1 in the presence of 1 equivalent of TMSOTf the reaction did not proceed at all, after the usual work-up only acetophenone and benzylcarbamate (*i.e.*, hydrolysis of **2a**) were observed. It is also worth noting that the TMS-enolate of acetopheneone was subjected to the same reaction conditions as those given in Table 1, entry 1 (*i.e.*, enecarbamate {NH-cbz} was substituted for TMS-enolate {$OSiMe_3$}), following acidic work-up diketone **4a** was isolated in 13% yield and 73% ee, that is ee is only a little lower for the TMS-enolate but the yield of the same product under the same conditions is greatly reduced.

Having established for, nickel(II) triflate mediated catalysis of enecarbamate additions to a symmetrical dimethyl ketone **1a**,

that longer reaction times can provide significant improvements in yield and slight improvements in ee, and that enecarbamate **2a** is a better acetophenone-enolate analogue than the corresponding TMS-enolate, we next examined the unsymmetrical diketone, pentane-2,3-dione **1b**, under the same reaction conditions as Table 1 entry 1 and Table 2 entry 16 (see Scheme 2).




**Scheme 2** Aldol-like reaction of enecarbamate **2a** with diketone **1b**; effect of long reaction time.

For the same reaction conditions as for the formation of **4a** a much more dramatic increase in overall yield of the two products (**4d** & **4e**) was observed, *i.e.*, 19% overall yield for a 48 h reaction increases to >99% combined yield for the analogous 14 d reaction. However it should be noted that no corresponding increase in ee was observed, the minor product's ee was reduced by 20%, the major product's ee was only 1% lower. Also that selectivity between addition to the ethyl or methyl ketone is reduced a little for longer reaction times (8.5 : 1 *versus* 7.0 : 1 respectively).

The non-linear effect of ligand ee was examined with respect to catalyst **6a**, for the formation of **4a**. The *in situ* catalyst preparation was carried out with mixtures of racemic and single enantiomer (*R*,*R*)-**5**, reactions were performed under the same conditions as that given in Table 1, entry 1 accept stock solutions of ligand were added. Fig. 1 shows the relationship between ligand and product enantiomeric excesses, a strong positive non-linear effect was observed.

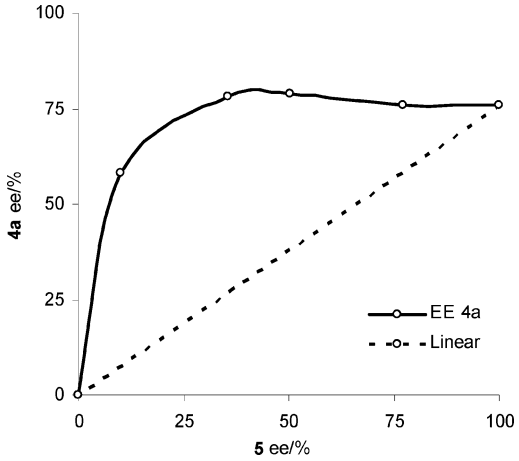
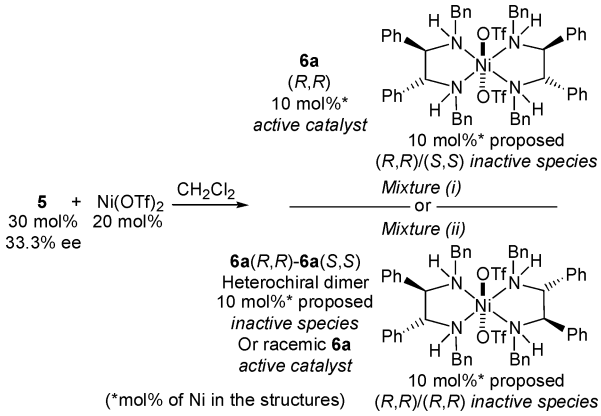



**Fig. 1** Non-linear effect of ligand **5** in reactions under the same conditions as Table 1, entry 1.

Enantiomeric excess of **5** and yield of product **4a** follows the approximate trend that lower ee gives lower yield (see supplementary information). That a strong positive non-linear effect was observed, is good evidence for the favourable formation of heterochiral bis-chelated $Ni(OTf)_2$ complexes or heterochiral dimers of complex **6a**, and that these structures are not active catalysts. Since use of excess ligand served to reduce the efficacy of a catalyst prepared from single enantiomer **6a** (ee and yield were reduced) we surmised bis-chelated metal complexes were likely the origin of deactivation, although this would necessitate the presence of free $Ni(OTf)_2$ in the non-linear effect experiments and hence a non-chiral pathway might be observed.

In order to clarify this further an experiment was performed employing 30 mol% of 33.3% ee ligand in combination with 20 mol% nickel(II) triflate, two proposed outcomes are given in Scheme 3.

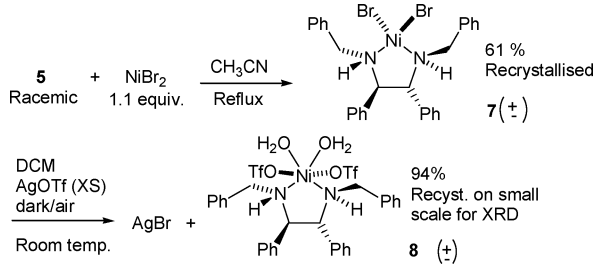



**Scheme 3** Proposed outcomes of mixing excess low ee ligand and $Ni(OTf)_2$.

Use of this catalyst mixture resulted in isolation of **4a** in 72% ee and 47% yield, that is ee is approximately the same as Table 1, entry 1 but the yield is reduced, suggesting that the same active catalyst species is present but to a lesser extent than in the 10 mol% single enantiomer case.

Using the same conditions as Scheme 3 the reaction was repeated with slightly higher ee **5** (50% ee), in this case product **4a** was obtained in an improved 75% yield and the ee remained almost unchanged (74% ee). More active catalyst is present with 50% ee ligand yet no reduction in ee was observed which implies the lack of a competitive achiral pathway. These results lead us to tentatively suggest that the formation of 2 : 1 *R*,*R* : *S*,*S* trimeric structures, similar to the TMEDA complexes previously reported,[3c] also play a role in a complicated deactivation equilibrium in the large non-linear effect we observed. To elucidate this and/or related structures by XRD or other means is currently the focus of attention for this program of research, we hope to report more details regarding this at a later date.

To date, elucidation of the anhydrous catalyst structure **6a** by single crystal X-ray diffraction has not proved successful. However, a racemic model for the binding of **5** to Ni(II) (the corresponding Ni(II) bromide complex **7**) was easily synthesized. Compound **7** was converted, *via* a non-anhydrous silver triflate mediated halide abstraction, to the bis-*aquo* complex **8** (see Scheme 4). Compound **8** was successfully crystallised from $CH_2Cl_2$–hexane–$Et_2O$ after many trials (see Fig. 2).‡ Other than identifying the almost complete absence of **5**, no useful NMR data could be obtained from **7** or **8**.




**Scheme 4** Synthesis of a nickel(II) bromide complex of a racemic diamine ligand and subsequent halide abstraction.

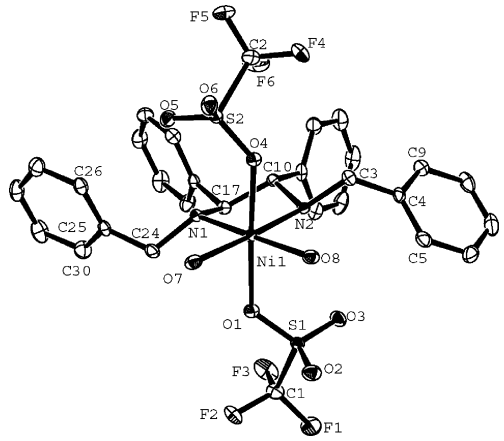



**Fig. 2** Representation of the crystal structure of **8**, protons omitted for clarity. Selected bond distances (Å), angles (°) and torsions (°): Ni(1)–O(1) = 2.107(1), Ni(1)–O(4) = 2.105(1), Ni(1)–O(7) = 2.044(1), Ni(1)–O(8) = 2.084(1), Ni(1)–N(1) = 2.075(1), Ni(1)–N(2) = 2.083(1), O(8)–Ni(1)–O(7) = 89.17(5), N(2)–Ni(1)–N(1) = 85.08(5), N(2)–C(10)–C(17)–N(1) = 53.7(2).

The crystal structure of **8** (Fig. 2) shows an octahedral nickel(II) complex where the two triflate moieties are bound directly to the metal, the ligand is bound equatorially, and two equatorial ancillary water ligands completed the octahedron. This is in contrast to a related nickel(II) bisoxazoline complex reported by Evans *et al.* where a square pyramidal structure was observed, one triflate was bonded with nickel(II) the other was more dissociated (in the solid state).[7a] It is likely that the flexibility of the benzyl arms of ligand **5** allow for satisfactory completion of the octahedron about nickel, maintaining a $C_2$ environment at the metal. Efficient chiral relay through the amino nitrogens upon coordination was also confirmed for compound **8** (see supplementary information for more details).

Owing to the novelty of nickel(II) catalysed enecarbamate additions to carbonyls further studies into improved activity and selectivity of nickel(II) are underway in our laboratory. Altering the electronic properties of the metal by changing the ligand or counter ion might facilitate the higher turnover frequencies desirable for a broadly applicable catalytic system.

## Acknowledgements

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## Notes and references

‡ CCDC reference numbers 269067. See http://dx.doi.org/10.1039/b505404d for crystallographic data in CIF or other electronic format.

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4 Overnight pre-mixing of ligand and metal triflate at rt was performed.
5 Conditions were selected based on previous work, see reference 1*a*.
6 That structure **3a** was formed initially was confirmed by $^1$H NMR spectroscopy in $d_6$-benzene of the crude reaction product and accurate mass spectroscopy (Found: $[M + H]^+$, $m/z$, (ESI) 340.1606. $C_{20}H_{22}NO_4$ requires 340.1549).
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8 See references 7*b–c*.
9 See reference 3*c*.
10 Observed rate constant, $k_{obsd}$, determined by plotting $-\ln([E]/[E]_0)$ *versus* time/s (E = enecarbamate **2a**, [E] determined by $^1$H NMR spectroscopy, see supplementary information). Half-life (h), $t_{\frac{1}{2}} = \ln 2/(k_{obsd} \times 3600)$.
11 The requirement for diketone chelation was demonstrated by use of acetophenone or butanone as substrates, 10 mol% loading of **6a** at 0 °C for 48 h, none and <5% conversion was observed respectively (confirmed by $^1$H NMR spectroscopy only).
12 D. A. Evans, C. S. Burgey, M. C. Kowalski and S. W. Tregay, *J. Am. Chem. Soc.*, 1999, **121**, 686.

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# Highly diastereo- and enantioselective reactions of enecarbamates with an aldehyde

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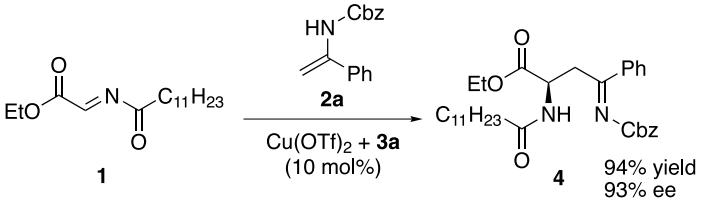
**Abstract**—Catalytic asymmetric addition reactions of enecarbamates with ethyl glyoxylate have been developed using $CuClO_4 \cdot 4CH_3CN$ and a diimine ligand as the catalyst. Highly diastereo- and enantioselective addition reactions of α-mono-substituted enecarbamates have been also achieved. These reactions afforded the corresponding adducts with high selectivity; that is, *syn* adducts from *Z*-enecarbamates and *anti* adducts from *E*-enecarbamates. The proposed reaction mechanism is an aza-ene type pathway, where the proton of an enecarbamate's N–H group plays an important role, not only for accelerating the reaction but also for providing a transition state suitable for the highly selective chiral induction.

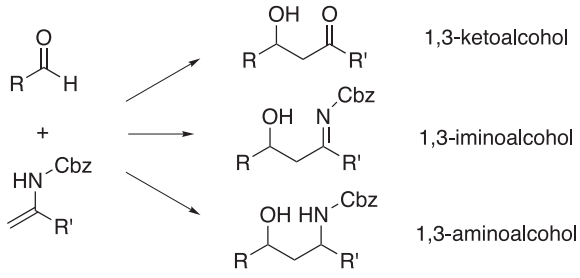

## 1. Introduction

Enamides and enecarbamates are potentially useful nucleophiles, which bear amide and carbamate moieties after undergoing nucleophilic additions. While enamides are readily prepared,[1] are easy to handle, and can be stored at room temperature, their use in organic synthesis is limited.[2] Recently, we have reported the first catalytic enantioselective addition of enamides and enecarbamates to imines, which afforded imine **4** in high yield with high selectivity (Scheme 1).[3] A $C_2$-symmetric copper catalyst prepared from $Cu(OTf)_2$ and diamine ligand **3a**, derived from 1,2-diphenyl ethylenediamine, catalyzed the reaction efficiently.[4] Imine **4** is a versatile compound, which can be converted into 1,3-diamides, 5-membered lactams, 3-keto 1-amides, etc. The use of aldehydes instead of imines as substrates for this reaction might lead to 1,3-ketoalcohols, 1,3-iminoalcohols, and 1,3-aminoalcohols, etc.




**Scheme 1.**

The objective of this research effort is to investigate the reactions of enamides with aldehydes.[5] The reaction of ethyl glyoxylate with enecarbamates would lead to products which have α-hydroxy γ-imino ester functionalities (Scheme 2). In the absence of a Lewis-acid catalyst, the reaction of ethyl glyoxylate (1.2 equiv.) with enecarbamate **2a** (1.0 equiv.) proceeded at 0 °C for 1.5 h to give **6a**, which was hydrolized to **7a** by treatment with HBr aq. (13% yield,




**Scheme 2.**

*Keywords*: Enamide; Enecarbamate; Asymmetric catalysis; Aza-ene reaction; Copper; N ligands.
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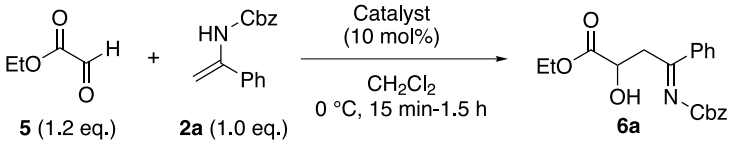
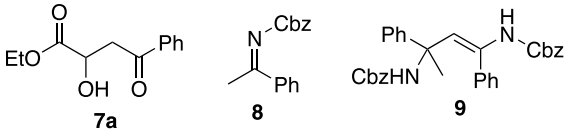
**Table 1.** Reaction of enecarbamate **2a** with ethyl glyoxylate (**5**). Initial results




**5** (1.2 eq.) **2a** (1.0 eq.) **6a**

| Entry | Catalyst | Yield (%)[a] | ee (%) |
|---|---|---|---|
| 1 | None | 13 | — |
| 2 | $Cu(OTf)_2$ | 18 | — |
| 3 | $CuClO_4 \cdot 4CH_3CN$ | 67 | — |
| 4 | $Sc(OTf)_3$ | 40 | — |
| 5 | $Yb(OTf)_3$ | 59 | — |
| 6[b] | $Cu(OTf)_2$ + **3a** | 93 | 55 |



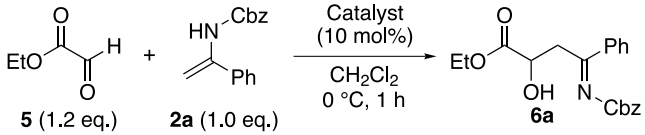

**7a** **8** **9**

[a] Yield of **7a** following an acidic work-up.
[b] 15 min.

entry 1 in Table 1). Use of copper (II) triflate as a catalyst (10 mol%) resulted in the formation of **8** and **9**, which indicated that an equilibrium between **2a** and **8** existed under Lewis acidic conditions and caused a self-coupling reaction between **2a** and **8** to form **9** (ca. 30% yield, entry 2 in Table 1). A similar phenomenon was observed when other Lewis acids such as $CuClO_4 \cdot 4CH_3CN$, $Sc(OTf)_3$, and $Yb(OTf)_3$ were employed as catalysts (entries 2–5 in Table 1). It is noted that a complex derived from $Cu(OTf)_2$ and diamine ligand **3a** did not accelerate the formation of **8** from **2a** at all, and that **7a** was isolated in high yield with modest enantioselectivity (93% yield, 55% ee, entry 6 in Table 1). This result would be attributed to lower Lewis acidity of the copper coordinated to diamine ligand **3a**.

These results prompted us to screen various metals in the presence of a range of diamine ligands, and the results are summarized in Table 2. The use of $Sc(OTf)_3$, $CoCl_2$, or $Zn(OTf)_2$ was found to accelerate the reaction of enecarbamates with ethyl glyoxylate selectively (58–86% yields), and in these cases the enecarbamate self-coupling

**Table 2.** Reaction of enecarbamate **2a** with **5** using various catalysts




**5** (1.2 eq.) **2a** (1.0 eq.) **6a**

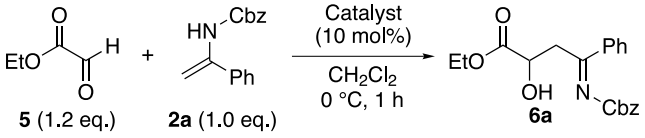
| Entry | Metal | Ligand | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | **3a** | 93 | 55 |
| 2 | $CuClO_4 \cdot 4CH_3CN$ | **3a** | 90 | 35 |
| 3 | $LiClO_4$ | **3d** | 21 | 0 |
| 4 | NaOTf | **3d** | Trace | — |
| 5 | $Mg(OTf)_2$ | **3b** | 5 | 38 |
| 6 | $Sc(OTf)_3$ | **3d** | 58 | 28 |
| 7 | $Sc(OTf)_3$ | **3h** | 60 | 1 |
| 8 | $FeCl_2$ | **3d** | 38 | 2 |
| 9 | $CoCl_2$ | **3d** | 77 | 2 |
| 10 | $CoCl_2$ | **3h** | 73 | 1 |
| 11 | $Zn(OTf)_2$ | **3a** | 86 | 39 |
| 12 | $Zn(OTf)_2$ | **3i** | 62 | 16 |
| 13 | $AgSbF_6$ | **3i** | 14 | 18 |
| 14 | AgOTf | **3i** | 31 | 35 |
| 15 | $Sn(OTf)_2$ | **3d** | 44 | 8 |
| 16 | $La(OTf)_3$ | **3d** | 70 | 0 |
| 17 | $Ce(OTf)_3$ | **3d** | 68 | 0 |
| 18 | $Pr(OTf)_3$ | **3d** | 61 | 0 |
| 19 | $Nd(OTf)_3$ | **3d** | 74 | 2 |
| 20 | $Sm(OTf)_3$ | **3d** | 72 | 0 |
| 21 | $Sm(OTf)_3$ | **3i** | 65 | 2 |
| 22 | $Sm(OTf)_3$ | **3h** | 88 | 0 |
| 23 | $Ho(OTf)_3$ | **3d** | 66 | 0 |
| 24 | $Yb(OTf)_3$ | **3b** | 40 | 2 |
| 25 | $Lu(OTf)_3$ | **3d** | 53 | 6 |

compound **9** was not observed. Ag (I) and Sn (II) salts were less active catalysts for this reaction. When various lanthanide salts were employed as catalysts (entries 16–25 in Table 2) in the presence of diamine ligand (commonly **3d**), the desired adducts were formed in moderate to high yields (40–88% yields), albeit enantioselectivities were negligible (<6% ee).

The copper complexes showed the best catalytic activity in this reaction, which led to the selection of Cu (I) and (II) in the parallel screening of ligand types. Diamine ligands **3a–f** derived from diphenyl ethylenediamine, box-type ligands **3g** and **3h**, diimine ligands **3i–3t** derived from cyclohexyl diamine, and diamine ligands **3v–3x** derived from cyclohexyl diamine were all used in conjunction with the Cu (I) and Cu (II). Among Cu (II) complexes (Table 3), a complex prepared from $Cu(OTf)_2$ and box ligand **3h** gave the highest enantioselectivity (73% ee).[6]

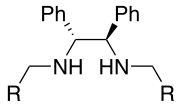
Preliminary tests using $CuClO_4 \cdot 4CH_3CN$ as a Lewis acid revealed that a catalyst derived from Cu (I) and diimine ligand **3i** exhibited good facial discrimination (entry 2 in Table 4, 93% ee).[7] Alternate counter anions $^{-}PF_6$ and $^{-}OTf$ gave adducts with lower selectivities (82% ee and 78% ee, respectively, entries 3 and 4 in Table 4). When 1-naphthyl and 2-naphthyl-substituted ligands **3j** and **3k** were examined (entries 5 and 6 in Table 4), moderate enantioselectivities were observed (73% ee and 68% ee,

**Table 3.** Reactions of enecarbamate **2a** with **5** using various copper(II) catalysts

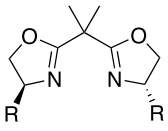



**5** (1.2 eq.) **2a** (1.0 eq.) **6a**

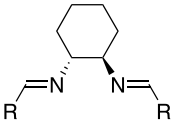
| Entry | Metal | Ligand | Yield (%) | ee (%)[a] |
|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | **3a** | 93 | 55 |
| 2[b] | $Cu(OTf)_2$ | **3a** | 91 | 54 |
| 3[c] | $Cu(OTf)_2$ | **3a** | 89 | 58 |
| 4 | $Cu(OTf)_2$ | **3b** | 74 | 59 |
| 5[d] | $Cu(OTf)_2$ | **3b** | 44 | 47 |
| 6 | $Cu(OTf)_2$ | **3c** | 58 | 57 |
| 7 | $Cu(OTf)_2$ | **3d** | 96 | 46 |
| 8 | $Cu(OTf)_2$ | **3e** | 97 | 37 |
| 9 | $Cu(OTf)_2$ | **3f** | 94 | 31 |
| 10 | $Cu(OTf)_2$ | **3g** | 85 | 31[a] |
| 11[c] | $Cu(OTf)_2$ | **3g** | 91 | 31[a] |
| 12 | $Cu(OTf)_2$ | **3h** | 70 | 73[a] |
| 13 | $Cu(OTf)_2$ | **3i** | 65 | 70 |
| 14 | $Cu(OTf)_2$ | **3j** | 66 | 28 |
| 15 | $Cu(OTf)_2$ | **3k** | 71 | 52 |
| 16 | $Cu(OTf)_2$ | **3l** | 68 | 17 |
| 17 | $Cu(OTf)_2$ | **3v** | 89 | 51 |
| 18 | $Cu(OTf)_2$ | **3w** | 91 | 50 |
| 19 | $Cu(OTf)_2$ | **3x** | Quant | 62 |
| 20 | $CuCl_2$ | **3a** | 47 | 17 |
| 21 | $CuCl_2$ | **3b** | 55 | 26 |
| 22 | $CuCl_2$ | **3i** | 50 | 19[a] |
| 23 | $Cu(SbF_6)_2$ | **3b** | 77 | 44 |



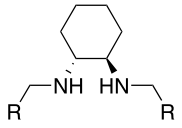

**3a:** R = 1-nap
**3b:** R = (3,5-($^t$Bu)$_2$)-Ph
**3c:** R = $^t$Bu
**3d:** R = Ph
**3e:** R = (*o*-F)-Ph
**3f:** R = (*o*-OMe)-Ph




**3g:** R = Ph
**3h:** R = $^t$Bu



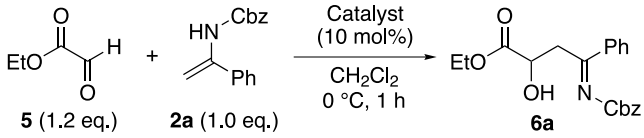

**3i:** R = Ph
**3j:** R = 1-nap
**3k:** R = 2-nap
**3l:** R = (3,5-di$^t$Bu)-$C_6H_3$
**3m:** R = *o*-Tol
**3n:** R = *m*-Tol
**3o:** R = *p*-Tol
**3p:** R = *p*-Et-$C_6H_4$
**3q:** R = *p*-$^i$Pr-$C_6H_4$
**3r:** R = *p*-F-$C_6H_4$
**3s:** R = *p*-Cl-$C_6H_4$
**3t:** R = *p*-Br-$C_6H_4$




**3v:** R = Ph
**3w:** R = 2-nap
**3x:** R = (3,5-($^t$Bu)$_2$)-Ph

[a] The absolute configuration is *R* except in entries 10–12 and 22 (*S*).
[b] Catalyst (30 mol%) was used.
[c] −20 °C.
[d] −78 °C.

**Table 4.** Reactions of enecarbamate **2a** with **5** using various copper(I) catalysts




**5** (1.2 eq.) **2a** (1.0 eq.) **6a**

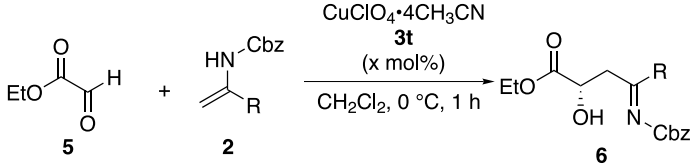
| Entry | Metal | Ligand | Yield (%) | ee (%)[a] |
|---|---|---|---|---|
| 1 | $CuClO_4 \cdot 4CH_3CN$ | **3a** | 90 | 35[a] |
| 2 | $CuClO_4 \cdot 4CH_3CN$ | **3i** | 94 | 93 |
| 3 | $CuPF_6 \cdot 4CH_3CN$ | **3i** | 94 | 82 |
| 4 | $CuOTf \cdot 0.5C_6H_5CH_3$ | **3i** | 66 | 78 |
| 5 | $CuClO_4 \cdot 4CH_3CN$ | **3j** | 92 | 73 |
| 6 | $CuClO_4 \cdot 4CH_3CN$ | **3k** | 52 | 68 |
| 7[b] | $CuClO_4 \cdot 4CH_3CN$ | **3i** | 48 | 91 |
| 8[c] | $CuClO_4 \cdot 4CH_3CN$ | **3i** | 97 | 93 |
| 9[d] | $CuClO_4 \cdot 4CH_3CN$ | **3i** | Quant | 94 |
| 10[d] | $CuClO_4 \cdot 4CH_3CN$ | **3m** | 97 | 81 |
| 11[d] | $CuClO_4 \cdot 4CH_3CN$ | **3n** | Quant | 86 |
| 12[d] | $CuClO_4 \cdot 4CH_3CN$ | **3o** | 98 | 95 |
| 13[d,e] | $CuClO_4 \cdot 4CH_3CN$ | **3o** | 20 | 17 |
| 14[d,f] | $CuClO_4 \cdot 4CH_3CN$ | **3o** | Trace | — |
| 15[d] | $CuClO_4 \cdot 4CH_3CN$ | **3p** | 87 | 94 |
| 16[d] | $CuClO_4 \cdot 4CH_3CN$ | **3q** | 93 | 94 |
| 17[d] | $CuClO_4 \cdot 4CH_3CN$ | **3r** | 97 | 96 |
| 18[d] | $CuClO_4 \cdot 4CH_3CN$ | **3s** | 93 | 96.5 |
| 19[d] | $CuClO_4 \cdot 4CH_3CN$ | **3t** | 93 | 97.0 |

[a] The absolute configuration is *S* except in entry 1 (*R*).
[b] −78 °C.
[c] Ethyl glyoxylate (1.5 equiv.) was used.
[d] Ethyl glyoxylate (2.0 equiv.) was used.
[e] Toluene was used as a solvent.
[f] Acetonitrile was used as a solvent.

respectively). The reaction catalyzed by a copper complex derived from $CuClO_4 \cdot 4CH_3CN$ and ligand **3i** proceeded at −78 °C to give a lower yield (48% yield, entry 7 in Table 4). Use of excess amounts of ethyl glyoxylate (1.5 and 2.0 equiv.) gave higher yields, 91% and quantitative yields, respectively (entries 8 and 9 in Table 4). Ligands bearing *para*-substituents on the phenyl arms led to higher enantiomeric excesses in the Cu (I)-catalyzed reaction (compare entry 12 with entries 2, 10 and 11 in Table 4). Finally, the Cu (I) complex of *para*-bromo ligand **3t** was found to give the highest stereoselectivity (97% ee, entry 19 in Table 4). The ligand **3t** gave rise to the best stereoselectivity in catalysis, presumably due to a strong steric contribution from the *para* substituent of the ancilary phenyl groups about the $C_2$ environment of the catalysts. Solvents other than dichloromethane were tested (toluene and acetonitrile, entries 13 and 14 in Table 4, respectively), but the catalytic activity of the resultant Cu (I) complexes was decreased significantly.

The optimal ligand, metal source, and solvent (**3t**, $CuClO_4 \cdot 4CH_3CN$ and $CH_2Cl_2$, respectively) were, therefore, employed in experiments where the loadings of both metal and ligand were reduced (entries 1–4 in Table 5). Only 1 mol% of the catalyst ($CuClO_4 \cdot 4CH_3CN$ 1 mol%, ligand **3t** 1.1 mol%) afforded **7a** in good yield with a slightly reduced enantiomeric excess (90% yield, 94% ee, entry 4 in Table 5). Other enecarbamates (**2b–e**) derived from

**Table 5.** Catalytic asymmetric reactions of various enecarbamates **2** with **5**




**5** **2** **6**

| Entry | **2** | *x* (mol%) | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | **2a** (R=Ph) | 10 | 93 | 97 |
| 2 | **2a** | 5 | 94 | 96 |
| 3 | **2a** | 2 | 96 | 95 |
| 4 | **2a** | 1 | 90 | 94 |
| 5 | **2b** (R=PMP) | 10 | 94 | 93 |
| 6 | **2c** (R=PCP) | 10 | 97 | 97 |
| 7 | **2d** (R=PMeP) | 10 | Quant | 96 |
| 8 | **2e** (R=2-Nap) | 10 | 91 | 96 |

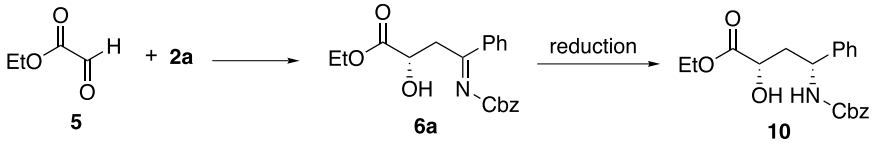
Cbz, benzyloxycarbonyl; PMP, *p*-methoxyphenyl; PCP, *p*-chlorophenyl; PMeP, *p*-methylphenyl; 2-Nap, 2-naphthyl.

aromatic ketones also reacted with ethyl glyoxylate to provide the corresponding adducts **7b–e** in high yields (91% to quant.) with high enantioselectivities (93–97% ee). It is noteworthy that all reactions were complete within only 1 h at 0 °C.

The Cu (I)-catalyzed protocol was able to furnish the potentially useful β-iminoalcohols in high ee, and subsequent reduction was then performed in order to demonstrate the utility of this enecarbamate process. Whilst the diastereoselective reduction of 1,3-ketoalcohols is well known,[8] there are relatively few reports concerning the diastereoselective reduction of 1,3-iminoalcohols.[9] Attempts for the selective reduction of **6a** are summarized in Table 6 (**6a** was prepared freshly as per entry 1 in Table 5). It has been previously reported that chelation of 1,3-ketoalcohols is often crucial for stereoselective reduction. Considering that β-iminoalcohols might coordinate in an analogous fashion, similar protocols were adopted. The use of $Zn(BH_4)_2$[8b] as a reducing agent resulted in around 60% yield with modest *syn*-selectivities. Reduction of **6a** did not proceed at −78 °C when $LiAlH(O^tBu)_3$[8g] was employed as a reductant, (**6a** was completely recovered). Sodium borohydride in the presence of $ZnCl_2$[10] at −78 °C gave benzylalcohol mainly, and only a trace amount of the desired product was observed (entry 5 in Table 6). Although benzylalcohol is assumed to be derived from the Cbz group attached to the nitrogen, the precise mechanism for the formation of benzylalcohol remains unclear. Additionally, K-selectride also formed a considerable amount of benzylalcohol even at −78 °C (entries 8–10 in Table 6), while L-selectride afforded the desired product in moderate yield (ca. 59% yield) with modest *anti*-selectivity (*syn*/*anti*=22/78, entry 11 in Table 6). Satisfactory selectivity was observed (*syn*/*anti*=94/6) when $NaBH_4$ was used in the presence of $Et_2B(OMe)$ which is known to aid chelation of 1,3-ketoalcohols in a THF/MeOH mixtures,[8d] and a slightly modified procedure was used (entry 13 in Table 6). Optimization studies showed that a threefold excess of reductants at −78 °C over 2 h afforded **10** in 65% yield with high *anti*-selectivity (94/6, entry 18 in Table 6). The relative configuration of **10** was assigned on the basis of NMR NOE experiments performed in the cyclic derivative **12** (Scheme 3).

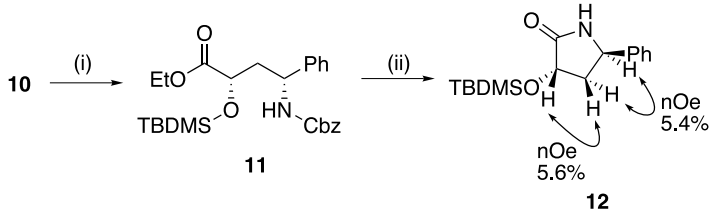
Diastereoselection in addition reactions of α-mono-substituted

**Table 6.** Selective reduction of **6a** into **10**

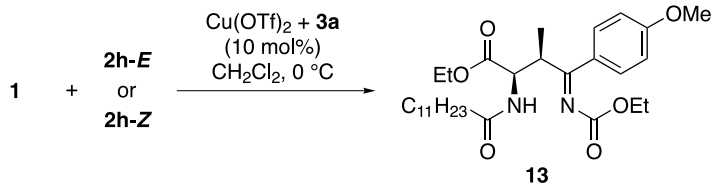



| Entry | Reagent (equiv.) | Additive (equiv.) | Solvent | Temperature | Time (h) | Yield (%)[a] | *syn*/*anti* |
|---|---|---|---|---|---|---|---|
| 1 | $Zn(BH_4)_2$ (1.0) | — | $Et_2O$ | −78 | 1 | <65 | 71/29 |
| 2 | $Zn(BH_4)_2$ (1.0) | — | $Et_2O$ | −78 | 3 | <66 | 78/22 |
| 3 | $Zn(BH_4)_2$ (1.0) | MS4A[b] | $Et_2O$ | −78 | 3 | <75 | 78/22 |
| 4 | $Zn(BH_4)_2$ (1.0) | — | Toluene–$Et_2O$[c] | −78 | 1 | <75 | 75/25 |
| 5 | $NaBH_4$ (2.0) | $ZnCl_2$ (1.5) | MeOH | −78 | 5.5 | Trace | — |
| 6 | $LiAlH(O^tBu)_3$ (5.0) | — | $Et_2O$ | −78 | 20 | Trace | — |
| 7 | $LiAlH(O^tBu)_3$ (5.0) | LiL (5.0) | $Et_2O$ | −78 | 20 | Trace | — |
| 8 | K-Selectride (2.2) | — | THF | −20 | 1.2 | 0 | — |
| 9 | K-Selectride (2.2) | — | THF | −45 | 4 | 0 | — |
| 10 | K-Selectride (2.2) | — | THF | −78 | 4 | 0 | — |
| 11 | L-Selectride (2.2) | — | THF | −20 | 16.5 | <59 | 22/78 |
| 12 | 9-BBN (3.0) | — | THF | −20 | 16.5 | Trace | — |
| 13 | $NaBH_4$ (2.2) | $Et_2B(OMe)$ (1.1) | THF–MeOH[d] | −78 | 3 | <60 | 94/6 |
| 14 | $NaBH_4$ (2.2) | $Et_2B(OMe)$ (1.1) | THF–MeOH[d] | −45 | 3 | <68 | 91/9 |
| 15 | $NaBH_4$ (2.2) | $Et_2B(OMe)$ (2.2) | THF–MeOH[d] | −78 | 5.5 | 55 | 91/9 |
| 16 | $NaBH_4$ (2.2) | $Et_2B(OMe)$ (2.2) | THF–MeOH[d] | −45 | 5.5 | 69 | 88/12 |
| 17 | $NaBH_4$ (2.2) | $Et_2B(OMe)$ (2.2) | THF–MeOH[e] | −78 | 2 | <37 | ND[f] |
| 18 | $NaBH_4$ (3.0) | $Et_2B(OMe)$ (3.0) | THF–MeOH[d] | −78 | 2 | 65 | 94/6 |

[a] The yields from **2**. A small amount of unknown compounds was contained except in entries 15, 16, and 18.
[b] 10 mg/0.1 mmol.
[c] Toluene/$Et_2O$=1/1.
[d] THF/MeOH=4/1.
[e] THF/MeOH=3/2.
[f] Not determined.



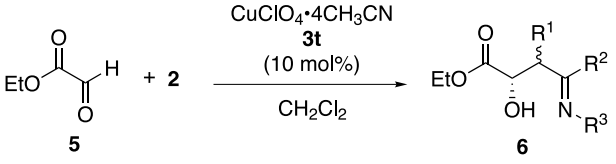

**Scheme 3.** (i) TBDMSOTf, 2,6-lutidine, $CH_2Cl_2$, 92% (ii) Pd/C, $H_2$, AcOH, AcOEt, quant



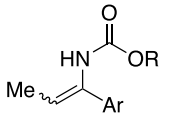

**Scheme 4.** **2h**–***E***: 77% y, *syn*/*anti*=86/14, 94% ee (*syn*) **2h**–**Z**: 63% y, *syn*/*anti*=68/32, 32% ee (*syn*)

enecarbamates with carbonyls is of great interest not only from a synthetic point of view but also from a mechanistic aspect. In our recent report *syn*-adducts were obtained from both (*E*)- and (*Z*)-enecarbamates **2h** and imine **1** catalyzed by a complex derived from Cu (II) and diamine ligand **3a** (Scheme 4).[3] Unlike their silicon enolate analogues, both geometric isomers of **2h** are stable on silica gel and separable by a standard chromatography technique. The α-substituted enecarbamate **2f** reacted with ethyl glyoxylate smoothly in the presence of $CuClO_4 \cdot 4CH_3CN$ and diimine ligand **3t** to afford **6f** in good yield (entries 1 and 4 in Table 7). It is noted that *anti*- and *syn*-adducts were obtained from the *E*- and *Z*-enecarbamates, respectively. The diastereoselectivities were excellent (*syn*/*anti*=1/99 and 98/2, respectively) and the enantiomeric excess of the major diastereomer was 98% ee in both cases. The same tendency on selectivity was observed for enecarbamates derived from *para*-substituted propiophenone (entries 7–12 in Table 7). The enecarbamates having an ethyl group at the α-position also gave similar diastereo- and enantioselectivities (entries 13 and 14 in Table 7). This reaction could be applied to aliphatic ketone-derived enecarbamates (entries 15–17 in Table 7). The reaction of enecarbamate **2l** derived from cyclohexanone afforded the desired product **6l** in good yield (85% yield) with slightly lower diastereoselectivity (*syn*/*anti*=16/84). Although prolonged reaction time (6–46 h) and lower temperature (−20 °C) were sometimes necessary, decrease of the catalyst loading

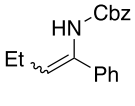
**Table 7.** Reactions of enecarbamates derived from α-substituted ketones



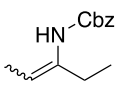

| Entry | 2 | Product | Yield (%)[a] | *syn*/*anti*[b] | Ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **2f***E* | **7f** | 83 | 1/99 | 98 |
| 2[d] | **2f***E*[e] | **7f** | 93 | 1/99 | 97 |
| 3[d] | **2f***E*[f] | **7f** | 95 | 1/99 | 98 |
| 4 | **2f***Z* | **7f** | 82 | 98/2 | 98 |
| 5 | **2f***Z*[e] | **7f** | 93 | 98/2 | 98 |
| 6 | **2f***Z*[f] | **7f** | 96 | 98/2 | 98 |
| 7 | **2g***E* | **7g** | 96 | 2/98 | 98 |
| 8 | **2g***Z* | **7g** | 97 | 98/2 | 98 |
| 9 | **2h***E* | **7g** | 82 | 3/97 | 96 |
| 10 | **2h***Z* | **7g** | 96 | 99/1 | 98 |
| 11 | **2i***E* | **7i** | 85 | 2/98 | 98 |
| 12 | **2i***Z* | **7i** | 79 | 99/1 | 98 |
| 13 | **2j***E*[g] | **7j** | 58 | 1/99 | 98 |
| 14 | **2j***Z* | **7j** | 92 | 99/1 | 98 |
| 15[d] | **2k***E* | **7k** | 83 | 3/97[h] | 97 |
| 16[d] | **2k***Z* | **7k** | 89 | 92/8[h] | 98 |
| 17 | **2l** | **7l** | 85 | 16/84[h] | 94 |



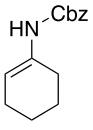

**2f**: Ar = Ph, R = Bn
**2g**: Ar = PMP, R = Bn
**2h**: Ar = PMP, R = Et
**2i**: Ar = PCP, R = Bn




**2j**

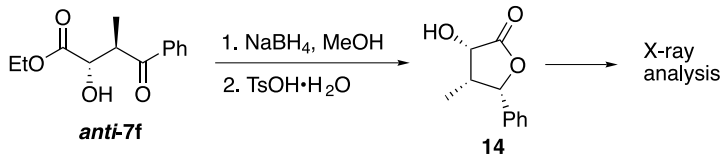



**2k**




**2l**

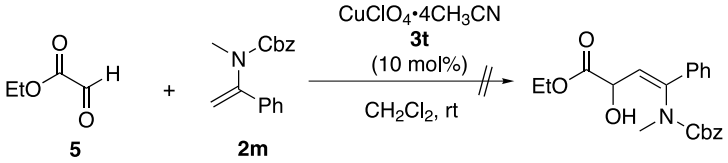
[a] Isolated yield of ketone product.
[b] Determined by HPLC.
[c] Ee of the major diastereomer, determined by HPLC.
[d] −20 °C.
[e] 1 mol% of catalyst was used.
[f] 0.1 mol% of catalyst was used.
[g] **5** (1.0 equiv.) and **2** (2.0 equiv.) were used.
[h] Determined by NMR analysis.




**Scheme 5.**

gave slightly better yields as shown in entries 1–6 of Table 7. Thus, the (*E*)- and (*Z*)-enecarbamates **2f** reacted with ethyl glyoxylate in the presence of only 0.1 mol% of the catalyst to afford the corresponding adducts in excellent yield (95 and 96%, respectively) with high diastereoselectivity (*syn*/*anti*=1/99 and 98/2, respectively) and enantioselelctivity (98% ee in both cases). The relative configuration of adduct **7f** was determined by the X-ray crystal structure analysis of **14**, which was synthesized from **7f** by reduction and subsequent cyclization in one pot (Scheme 5). The relative configuration of other adducts, general formula **7**, was determined by an analogy of the $^1$H NMR spectrum of **7f**.

In a bid to elucidate the reaction mechanism, enecarbamate **2m**, which has a tertiary amide moiety, was used to assess the role of the proton attached to the nitrogen. It was interesting to find that no reaction occurred in the presence of 10 mol% of the catalyst even at room temperature (Scheme 6). That the reaction proceeded stereospecifically when α-substituted enecarbamates bear N–H functionalities suggests a concerted aza-ene type reaction mechanism;[11] that is, a hydrogen atom attached to the nitrogen of enecarbamates would accelerate the reaction rate considerably through an intramolecular hydrogen transfer pathway. Two possible modes of a nucleophilic attack exist; an open transition state model or a concerted 6-membered ring fashion. Possible open transition states are shown in Figure 1; *E*-enecarbamates are used in TS-1 and TS-2, while *Z*-enecarbamates are used in TS-3 and TS-4. The steric interaction between the methyl group at the α-position of an enecarbamate and the copper complex is believed to be large, TS-2 would be favorable over TS-1. Similarly, since TS-3 would predominate over TS-4, *syn*-adducts are obtained in both cases. This contradicts the experimental results (*syn*-products from *Z*-enecarbamates, *anti*-products from *E*-enecarbamates). Possible concerted cyclic transition states are shown in Figure 2; TS-5 and TS-7 are derived from *Z*-enecarbamates, TS-6 and TS-8 are derived from *E*-enecarmates. In TS-7 and TS-8, since the steric interaction between the R group of enecarbamates and ethyl glyoxylate would be large, TS-5 and TS-6 are believed to predominate over TS-7 and TS-8, respectively. This explains the observed stereoselectivity and the role of the




**Scheme 6.**

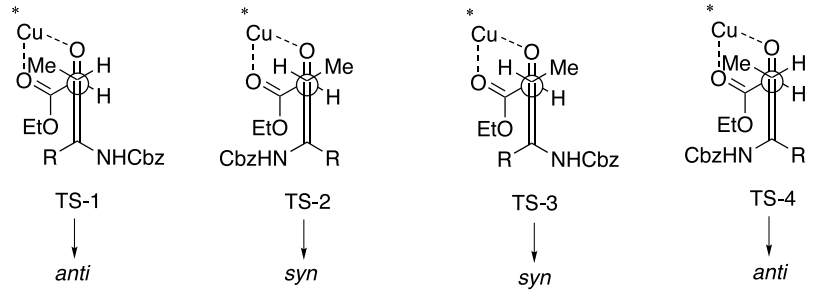



**Figure 1.** Possible acyclic transition state models.

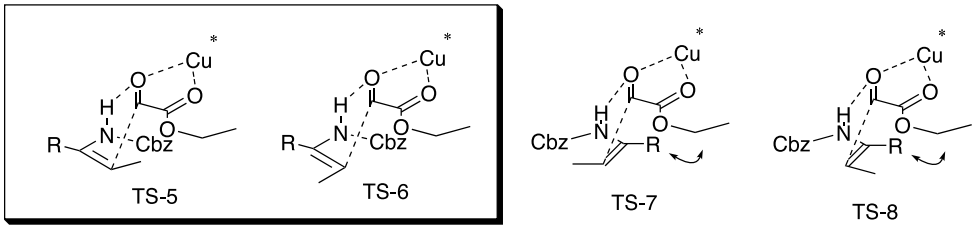



**Figure 2.** Possible cyclic transition state models.

N–H proton of enecarbamates. Attempts to crystallize model systems for X-ray diffraction are now under way.

In conclusion, catalytic asymmetric addition reactions of enecarbamates with ethyl glyoxylate have been developed using $CuClO_4 \cdot 4CH_3CN$ and diimine ligand **3t** as a catalyst. The products were 1,3-iminoalcohols, which were converted to the corresponding 1,3-amidealcohols diastereoselectively, employing $NaBH_4$ and $Et_2B(OMe)$ in the reduction. We have also developed highly diastereo- and enantioselective addition reactions of α-mono-substituted enecarbamates. These reactions afforded the corresponding adducts with high selectivity; that is, *syn* adducts from *Z*-enecarbamates and *anti* adducts from *E*-enecarbamates. The reaction proceeded smoothly in the presence of only 0.1 mol% of the catalyst to afford 1,3-iminoalcohols in high yields with high diastereo- and enantioselectivities. Aromatic ketone-derived enecarbamates as well as those derived from aliphatic and cyclic ketones were also found to be good substrates. The proposed reaction mechanism is an aza-ene type pathway, where the proton of an enecarbamate's N–H group plays an important role, not only accelerating the reaction but also providing a transition state suitable for the highly selective chiral induction.

## 2. Experimental

### 2.1. General

Melting points are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard ($\delta=0$) for $^1H$ NMR, and $CDCl_3$ was used as internal standard ($\delta=77.0$) for $^{13}C$ NMR. IR spectra were measured with a JASCO FT/IR-610. Optical rotations were measured with a JASCO P-1010 polarimeter. High-performance liquid chromatography was carried out using following apparatuses; SHIMADZU LC-10AT (liquid chromatograph), SHIMADZU SPD-10A (UV detector), and SHIMADZU C-R6A Chromatopac. Gas chromatography and mass spectrometry analysis were carried out using the following apparatuses; SHIMADZU GC-17A, SHIMADZU GCMS-QP5050A. Column chromatography was conducted on Silica gel 60 (Merck), and preparative thin-layer chromatography was carried out using Wakogel B-5F. All reactions were carried out under argon atmosphere in dried glassware. All solvents were dried and distilled by standard procedures. Enecarbamates **2a–j** were prepared according to the method reported by Kagan et al.[1a] Enecarbamates **2k** and **2l** were prepared by using a modified procedure reported by Machida et al.[1b,12] Enecarbamate **2m** was prepared from **2a**. Diamine ligands **3a–f** were prepared according to the reported method.[4b] Diimine ligands **3i–t** were prepared from commercially available (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate according to the reported method.[13] Diamine ligands **3v–x** were prepared by reduction of **3i**, **3k**, and **3l**, respectively using $NaBH_4$ in MeOH.

## 3. Enecarbamates

### 3.1. Analytical data for enecarbamates 2a–j

**3.1.1. (1-Phenyl-vinyl)-carbamic acid benzyl ester (2a).** Mp 69.4–69.5 °C; $^1H$ NMR ($CDCl_3$) $\delta=4.96$ (s, 1H), 5.16 (s, 2H), 5.63 (s, 1H), 6.33 (s, 1H), 7.25–7.45 (m, 10H); $^{13}C$ NMR ($CDCl_3$) $\delta=67.0$, 99.6, 126.0, 128.3, 128.5, 128.6, 128.7, 136.0, 138.1, 140.5, 153.7; IR (neat) 3310, 3060, 3033, 1739, 1701, 1634, 1523, 1452, 1227, 1125, 1063, 857, 772, 740, 696, 596 $cm^{-1}$; HRMS (EI). Exact mass calcd for $C_{16}H_{15}NO_2$ $[M]^+$, 253.1103. Found 253.1093. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.77; H, 6.16; N, 5.52.

**3.1.2. [1-(4-Methoxy-phenyl)-vinyl]-carbamic acid benzyl ester (2b).** Mp 54.7–54.8 °C; $^1H$ NMR ($CDCl_3$) $\delta=3.81$ (s, 3H), 4.89 (d, 1H, $J=1.0$ Hz), 5.18 (s, 2H), 5.54 (s, 1H), 6.26 (s, 1H), 6.85–6.90 (m, 2H), 7.30–7.40 (m, 7H); $^{13}C$ NMR ($CDCl_3$) $\delta=55.3$, 66.9, 98.4, 113.9, 127.2, 128.3, 128.5, 130.6, 136.0, 140.1, 153.7, 160.0; IR (neat) 3330, 1736, 1632, 1608, 1509, 1456, 1219, 1179, 1126, 1063, 1030, 834, 742, 698 $cm^{-1}$; HRMS (EI). Exact mass calcd for $C_{17}H_{17}NO_3$ $[M]^+$, 283.1208. Found 283.1208. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.84; H, 6.09; N, 4.91.

**3.1.3. [1-(4-Chloro-phenyl)-vinyl]-carbamic acid benzyl ester (2c).** Mp 79.0–79.1 °C; $^1H$ NMR ($CDCl_3$) $\delta=4.96$ (s, 1H), 5.17 (s, 2H), 5.59 (s, 1H), 6.25 (s, 1H), 7.28–7.43 (m, 9H); $^{13}C$ NMR ($CDCl_3$) $\delta=67.1$, 100.6, 127.3, 128.3, 128.4, 128.6, 128.8, 134.6, 135.8, 136.5, 139.7, 153.6; IR (neat) 3299, 1699, 1532, 1239, 1059, 838, 741, 696 $cm^{-1}$; HRMS (EI). Exact mass calcd for $C_{16}H_{14}ClNO_2$ $[M]^+$, 287.0713. Found 287.0708. Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87. Found: C, 66.53; H, 5.02; N, 4.91.

**3.1.4. (1-*p*-Tolyl-vinyl)-carbamic acid benzyl ester (2d).** Mp 52.3–53 °C; $^1H$ NMR ($CDCl_3$) $\delta=2.34$ (s, 3H), 4.93 (s, 1H), 5.16 (s, 2H), 5.58 (s, 1H), 6.30 (s, 1H), 7.14 (apparent d, 2H, $J=7.8$ Hz), 7.25–7.40 (m, 7H); $^{13}C$ NMR ($CDCl_3$) $\delta=21.1$, 66.9, 98.8, 125.8, 128.3, 128.5, 129.3, 135.3, 136.0, 138.7, 140.4, 153.7; IR (neat) 3398, 3327, 3032, 1736, 1361, 1508, 1454, 1383, 1321, 1219, 1124, 1063, 955, 852, 825, 735 $cm^{-1}$; LRMS (FAB) $m/z=268$ ($M+H^+$); Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.20; H, 6.48; N, 5.21.

**3.1.5. (1-Naphthalen-2-yl-vinyl)-carbamic acid benzyl ester (2e).** Mp 100.3–101.5 °C; $^1H$ NMR ($CDCl_3$) $\delta=5.11$ (s, 1H), 5.19 (s, 2H), 5.72 (s, 1H), 6.45 (s, 1H), 7.30–7.60 (m, 8H), 7.76–7.86 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta=67.1$, 100.4, 124.0, 124.7, 126.5, 127.6, 128.2, 128.3, 128.4, 128.6, 133.1, 133.3, 135.3, 135.9, 140.5, 153.8; IR (neat) 3282, 3046, 1701, 1622, 1527, 1226, 1106, 1064, 968, 884, 827, 694, 583 $cm^{-1}$; HRMS (EI). Exact mass calcd for $C_{20}H_{17}NO_2$ $[M]^+$, 303.1259. Found 303.1251. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.49; H, 5.82; N, 4.64.

**3.1.6. (*Z*)-(1-Phenyl-propenyl)-carbamic acid benzyl ester (2f*Z*).** Mp 73.5–74.0 °C; $^1H$ NMR ($CDCl_3$) $\delta=1.79$

(d, 3H, $J=6.8$ Hz), 5.13 (s, 2H), 5.79 (q, 1H, $J=6.8$ Hz), (6.00 (brs, 1 H), 7.00–7.62 (m, 10 H); $^{13}$C NMR ($C_6D_6$) $\delta=$ 13.5, 67.0, 119.5, 126.0, 127.7, 128.5, 128.5, 135.0, 137.1, 139.2; IR (neat) 3385, 3296, 3032, 2941, 1701, 1498, 1452, 1399, 1329, 1225, 1089, 1018, 916, 824, 760, 695 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1339.

**3.1.7. (*E*)-(1-Phenyl-propenyl)-carbamic acid benzyl ester (2f*E*).** Mp 63.9–64.0 °C; $^1$H NMR ($CDCl_3$) $\delta=1.70$ (d, 3H, $J=7.3$ Hz), 5.11 (s, 2H), 5.90–6.25 (br, 2H), 7.20–7.50 (m, 10H); $^{13}$C NMR ($C_6D_6$) $\delta=13.7$, 66.7, 112.0, 128.0, 128.1, 128.5, 128.5, 128.6, 129.1, 134.6, 137.0, 137.2, 153.9; IR (neat) 3398, 3316, 3032, 2938, 1713, 1516, 1449, 1393, 1328, 1213, 1137, 1033, 922, 835, 771, 739, 699, 587 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1347.

**3.1.8. (*Z*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid benzyl ester (2g*Z*).** Mp 110–110.5 °C; $^1$H NMR ($CDCl_3$) $\delta=1.77$ (d, 3H, $J=6.9$ Hz), 3.80 (s, 3H), 5.14 (s, 2H), 5.68 (q, 1H, $J=6.9$ Hz), 5.96 (brs, 1H), 6.84 (apparent d, 2H, $J=8.8$ Hz), 7.32 (m, 7H); $^{13}$C NMR ($C_6D_6$) $\delta=13.5$, 54.8, 66.9, 114.0, 117.6, 127.2, 128.5, 131.8, 134.6, 137.2, 154.1, 159.8; IR (neat) 3305, 3039, 2945, 2843, 1709, 1611, 1509, 1452, 1400, 1334, 1294, 1247, 1176, 1089, 1029, 820, 742, 699, 590 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$, 298.1443. Found 298.1435.

**3.1.9. (*E*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid benzyl ester (2g*E*).** Mp 66.0–66.5 °C; $^1$H NMR ($CDCl_3$) $\delta=1.69$ (d, 3H, $J=7.1$ Hz), 3.82 (s, 3H), 5.11 (s, 2H), 5.80–6.15 (m, 2H), 6.85–6.95 (m, 2H), 7.20–7.50 (m, 7H); $^{13}$C NMR ($C_6D_6$) $\delta=13.8$, 54.7, 66.6, 111.1, 114.0, 128.1, 128.5, 128.6, 129.5, 130.3, 134.4, 137.1, 153.9, 159.7; IR (neat) 3323, 3033, 2941, 2843, 1719, 1609, 1509, 1296, 1247, 1177, 1135, 1027, 840, 739, 697 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$, 298.1443. Found 298.1452.

**3.1.10. (*Z*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid ethyl ester (2h*Z*).** Mp 57.1–57.2 °C; $^1$H NMR ($CDCl_3$) $\delta=1.25$ (brs, 3H), 1.75 (d, 3H, $J=7.1$ Hz), 3.78 (s, 3H), 4.13 (q, 2H, $J=7.1$ Hz), 5.66 (q, 1H, $J=7.1$ Hz), 5.88 (brs, 1H), 6.80–6.85 (m, 2H), 7.28–7.36 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta=13.4$, 14.5, 55.2, 61.2, 113.6, 117.4, 126.7, 131.1, 133.9, 159.2; IR (neat) 3301, 2979, 1703, 1609, 1510, 1376, 1329, 1245, 1178, 1099, 1037, 824, 774, 594, 448 cm$^{-1}$; HRMS (EI). Exact mass calcd for $C_{13}H_{17}NO_3$ $[M]^+$, 235.1208. Found 235.1204. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.21; H, 7.32; N, 5.95.

**3.1.11. (*E*)-[1-(4-Methoxy-phenyl)-propenyl]-carbamic acid ethyl ester (2h*E*).** $^1$H NMR ($CDCl_3$) $\delta=1.11$ (t, 3H, $J=7.1$ Hz), 1.57 (d, 3H, $J=7.3$ Hz), 3.70 (s, 3H), 4.01 (q, 2H, $J=7.1$ Hz), 5.70–5.95 (m, 2H), 6.73–6.80 (m, 2H), 7.10–7.16 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta=13.7$, 14.5, 55.2, 60.8, 111.6, 113.6, 129.1, 129.9, 133.7, 154.3, 159.1; IR (neat) 3319, 2980, 1715, 1608, 1511, 1382, 1293, 1247, 1175, 1138, 1037, 836, 614, 499 cm$^{-1}$; HRMS (EI). Exact mass calcd for $C_{13}H_{17}NO_3$ $[M]^+$, 235.1208. Found 235.1201.

**3.1.12. (*Z*)-[1-(4-Chloro-phenyl)-propenyl]-carbamic acid benzyl ester (2i*Z*).** Mp 95.2–95.3 °C; $^1$H NMR ($C_6D_6$) $\delta=1.48$ (br, 3H), 5.02 (brs, 2H), 5.20–5.90 (br, 2H), 6.60–7.40 (m, 9H); $^{13}$C NMR ($C_6D_6$) $\delta=13.4$, 67.1, 119.8, 127.2, 128.3, 128.6, 133.4, 134.0, 136.9, 137.7, 153.8; IR (neat) 3292, 3033, 2947, 1706, 1589, 1494k 1398, 1327, 1299, 1094, 1016, 819, 741, 697 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{17}H_{17}ClNO_2$ $[M+H]^+$, 302.0948. Found 302.0936.

**3.1.13. (*E*)-[1-(4-Chloro-phenyl)-propenyl]-carbamic acid benzyl ester (2i*E*).** Mp 71.2–71.3 °C; $^1$H NMR ($C_6D_6$) $\delta=1.44$ (d, 3H, $J=7.4$ Hz), 5.02 (s, 2H), 5.47 (brs, 1H), 6.12 (brs, 1H), 6.70–6.80 (m, 2H), 6.95–7.25 (m, 7H); $^{13}$C NMR ($C_6D_6$) $\delta=13.5$, 66.8, 128.6, 128.6, 128.7, 130.4, 133.5, 133.8, 135.4, 136.9, 153.7; IR (neat) 3398, 3309, 3033, 2941, 1708, 1595, 1517, 1497, 1458, 1393, 1327, 1219, 1138, 1093, 1034, 836, 740, 701 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{17}H_{17}ClNO_2$ $[M+H]^+$, 302.0948. Found 302.0943.

**3.1.14. (*Z*)-(1-Phenyl-but-1-enyl)-carbamic acid benzyl ester (2j*Z*).** Mp 60.3–60.8 °C; $^1$H NMR ($C_6D_6$) $\delta=0.89$ (t, 3H, $J=7.1$ Hz), 2.03 (br, 2H), 5.04 (s, 2H), 5.30–5.55 (m, 2H), 7.00–7.25 (m, 8H), 7.28–7.36 (m, 2H); $^{13}$C NMR ($C_6D_6$) $\delta=13.6$, 21.6, 67.0, 126.1, 126.8, 127.4, 128.1, 128.5, 128.6, 133.5, 137.1, 139.2; IR (neat) 3294, 3033, 2961, 2876, 1705, 1498, 1458, 1400, 1334, 1223, 1092, 1026, 753, 691 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$, 282.1494. Found 282.1495.

**3.1.15. (*E*)-(1-Phenyl-but-1-enyl)-carbamic acid benzyl ester (2j*E*).** $^1$H NMR ($C_6D_6$) $\delta=0.87$ (t, 3H, $J=7.4$ Hz), 1.99 (quint, 3H, $J=7.4$ Hz), 5.01 (s, 2H), 5.56 (brs, 1H), 6.26 (brs, 1H), 6.95–7.25 (m, 10H); $^{13}$C NMR ($C_6D_6$) $\delta=$ 15.1, 21.0, 66.6, 118.8, 126.4, 126.9, 128.2, 128.5, 128.6, 128.6, 129.0, 133.6, 137.1, 137.5, 153.6; IR (neat) 3398, 3319, 3032, 2962, 2876, 1723, 1514, 1454, 1367, 1327, 1219, 1134, 1039, 984, 922, 857, 743, 698 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$, 282.1494. Found 282.1481.

### 3.2. Preparation and analytical data for enecarbamates 2k and 2l

**3.2.1. Enecarbamate 2k*E* and 2k*Z*.** To a solution of $NaN_3$ (1.675 g, 25.8 mmol) in $H_2O$ (12 mL) was added a solution of **15**[14] (2.85 g, 21.47 mmol) in THF (7 mL) dropwise at 0 °C. The mixture was vigorously stirred overnight and $Et_2O$ was added. After separation of the phases, the organic layer was washed with a saturated $Na_2CO_3$ aqueous solution and brine sequentially. $Et_2O$ was evaporated under reduced pressure of 300 mm Hg (Caution!) to give the crude adduct **16** in THF. This solution was added to boiling THF (10 mL) at 80 °C very slowly for over 1.5 h. After completion of the addition, the mixture was stirred at 80 °C until evolution of $N_2$ gas stopped (for about 2 h). The mixture was allowed to cool to room temperature (rt), and THF was evaporated at 100 mm Hg. The residue was distilled 2 times (65 °C, 100 mm Hg) to give pure **17** (1.113 g, 47% yield). Benzyl alcohol was added to **17** (1.113 g, 10.0 mmol) at −78 °C. The freezed reaction mixture was allowed to warm to rt for over 6 h, and was stirred until **17** was not detected in NMR

analysis (about over 3 days). The mixture was chromatogaphed on silica gel to afford geometric isomer **2k***Z* as a white solid (1.86 g, 85% yield). To a solution of **2k***Z* (237 mg, 1.079 mmol) in THF (12 mL) was added KO$^t$Bu (145.5 mg, 1.29 mmol) at rt. The reaction mixture was kept stirred for 14 h. The reaction was quenched by addition of a saturated $NH_4Cl$ aqueous solution at rt, and the product was extracted with $Et_2O$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel to afford almost 1:1 geometric mixture **2k** (184 mg, 78% yield). The mixture was separated by careful thin layer chromatography on silica gel (eluent: toluene/$Et_2O$=10/1) to afford geometric isomer **2k***E* (Scheme 7).

**3.2.2. Enecarbamate 2l.** According to the procedure mentioned above, **2l** was obtained. The boiling point of the corresponding isocyanate was 78 °C/40 mm Hg.

**3.2.3. (*Z*)-(1-Ethyl-propenyl)-carbamic acid benzyl ester (2k*Z*).** Mp 33.0–33.5 °C; $^1$H NMR ($C_6D_6$) $\delta$=0.79 (t, 3H, $J$=7.5 Hz), 1.45 (d, 3H, $J$=7.0 Hz), 1.95 (q, 2H, $J$=7.5 Hz), 5.04 (s, 2H), 5.38 (brs, 1H), 5.72 (q, 1H, $J$=7.0 Hz), 7.00–7.30 (m, 5H); $^{13}$C NMR ($C_6D_6$) $\delta$=11.9, 12.4, 22.7, 66.5, 128.2, 128.6, 128.6, 136.2, 137.3; IR (neat) 3322, 3064, 3033, 2969, 2935, 2877, 1706, 1523, 1455, 1380, 1351, 1307, 1234, 1097, 1029, 998, 831, 738 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$, 220.1338. Found 220.1347.

**3.2.4. (*E*)-(1-Ethyl-propenyl)-carbamic acid benzyl ester (2k*E*).** Mp 53.0–54.0 °C; $^1$H NMR ($C_6D_6$) $\delta$=0.95 (t, 3H, $J$=7.5 Hz), 1.28 (d, 3H, $J$=6.8 Hz), 2.34 (brq, 2H, $J$=7.5 Hz), 4.70 (q, 1H, $J$=6.8 Hz), 5.05 (s, 2H), 5.50 (brs, 1H), 7.00–7.26 (m, 5H); $^{13}$C NMR ($C_6D_6$) $\delta$=11.7, 12.6, 27.9, 66.7, 110.5, 128.2, 128.5, 128.6, 137.2, 137.3; IR (neat) 3305, 2967, 2751, 1693, 1515, 1450, 1321, 1257, 1108, 966, 848, 738, 698 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$, 220.1338. Found 220.1348.

**3.2.5. Cyclohex-1-enyl-carbamic acid benzyl ester (2l).** Mp 49.0–50.0 °C; $^1$H NMR ($C_6D_6$) $\delta$=1.26–1.45 (m, 4H), 1.70–1.80 (m, 2H), 1.86–1.98 (m, 2H), 5.03 (s, 2H), 5.31 (brs, 1H), 6.01 (brs, 1H), 7.00–7.25 (m, 5H); $^{13}$C NMR ($C_6D_6$) $\delta$=22.4, 22.8, 24.1, 27.7, 66.4, 109.3, 128.2, 128.6, 128.6, 132.3, 137.3, 153.2; IR (neat) 3322, 3058, 3033, 2931, 2838, 1706, 1538, 1452, 1380, 1348, 1305, 1232, 1062, 1037, 917, 840, 804, 736, 696 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{14}H_{18}NO_2$ $[M+H]^+$, 232.1338. Found 232.1342.

### 3.3. Preparation and analytical data for enecarbamte 2m

NaH (60%, 94.7 mg, 2.37 mmol) freshly washed with pentane was added to a flask, followed by addition of DMF (2.0 mL). The suspension was cooled to 0 °C, and **2a** (300 mg, 1.18 mmol) in DMF (3.0 mL) was added. The mixture was stirred for 30 min at rt, and then cooled to 0 °C. MeI (0.30 mL, 4.74 mmol) was added and the reaction mixture was stirred overnight at rt until the starting material disappeared. The reaction was quenched by addition of saturated aqueous $NH_4Cl$, and the aqueous layer was extracted with AcOEt. The organic layer was washed with water twice and brine, and then dried over $MgSO_4$. The solvents were evaporated and the residue was purified by chromatography on silica gel to afford **2m** (307.8 mg, 97% yield).

**3.3.1. Methyl-(1-phenyl-vinyl)-carbamic acid benzyl ester (2m).** Mp 34.0–35.0 °C; $^1$H NMR ($CDCl_3$) $\delta$=3.21 (s, 3H), 5.04 (s, 2H), 5.16 (s, 1H), 5.46 (s, 1H), 6.80–7.40 (m, 10H); $^{13}$C NMR ($CDCl_3$) $\delta$=37.6, 67.2, 110.0, 125.5, 127.5, 127.6, 128.2, 128.3, 128.5, 136.3, 137.2, 148.1, 155.5; IR (neat) 3032, 2954, 2888, 1703, 1626, 1446, 1389, 1337, 1203, 1146, 1027, 955, 902, 777, 696 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1349.

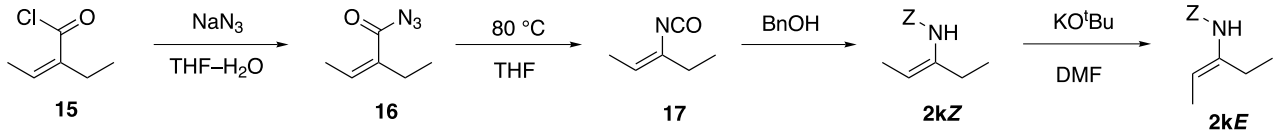
## 4. Typical procedure for distillation of ethyl glyoxylate

Ethyl glyoxylate was purchased from Tokyo Kasei Kogyo (TCI) as a polymer form in toluene. The ethyl glyoxylate toluene solution (30 g) was added to the flame dried flask. Toluene was evaporated completely under vacuum (<1 mm Hg) at rt, and $P_2O_5$ (ca. 300 mg) was added to the polymeric ethyl glyoxylate. The mixture was distilled to give almost-toluene-free monomeric ethyl glyoxylate as a slightly yellow liquid (150 mm Hg, 80 °C). Monomeric ethyl glyoxylate easily polymerizes within 30 min to give viscous liquid. Therefore, distilled ethyl glyoxylate should be used immediately after purification.

## 5. Addition reactions of enecarbamates to ethyl glyoxylate

### 5.1. Typical procedure for addition reactions of enecarbamates to ethyl glyoxylate using a chiral copper catalyst prepared from $CuClO_4\cdot 4CH_3CN$ and chiral diimine ligand 3t

Ligand **3t** (9.9 mg, 0.022 mmol) in $CH_2Cl_2$ (1.5 mL) was added to the $CuClO_4\cdot 4CH_3CN$ (6.5 mg, 0.020 mmol) flask under argon The yellow solution was stirred for over 12 h, and cooled to 0 °C. Freshly distilled ethyl glyoxylate (100 μL, 0.40 mmol) in $CH_2Cl_2$ (0.8 mL) was added to the mixture, and then enecarbamate **2** (0.20 mmol) in $CH_2Cl_2$ (0.8 mL) was added in one portion. The reaction mixture was stirred at 0 °C, and was quenched by addition of saturated aqueous $NaHCO_3$. The reaction mixture was allowed to warm to rt, and was extracted with $CH_2Cl_2$. The




**Scheme 7.**

organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the residue was dissolved in EtOH (3.0 mL), and a 48% HBr aqueous solution (0.3 mL) was added to the solution. The mixture was stirred at rt for 1.5 min, and then the reaction was quenched by addition of saturated aqueous $NaHCO_3$ at 0 °C. The reaction mixture was allowed to warm to rt. The mixture was extracted with $CH_2Cl_2$, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvents were evaporated, the crude product was purified by chromatography on silica gel to afford the desired compound **7**.

### 5.2. Analytical data for 7

**5.2.1. (2*S*)-2-Hydroxy-4-oxo-4-phenyl-butyric acid ethyl ester (7a).** $^1$H NMR ($CDCl_3$) $\delta$=1.27 (t, 3H, $J$=7.1 Hz), 3.29 (brs, 1H), 3.44 (dd, 1H, $J$=6.1, 17.6 Hz), 3.52 (dd, 1H, $J$=3.9, 17.6 Hz), 4.25 (q, 2H, $J$=7.1 Hz), 4.61–4.67 (m, 1H), 7.44–7.50 (m, 2H), 7.54–7.60 (m, 1H), 7.92–7.98 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$=14.0, 42.1, 61.8, 67.1, 128.1, 128.6, 133.5, 136.4, 173.7, 197.5. IR (neat) 3475, 3063, 2983, 1737, 1687, 1597, 1580, 1449, 1368, 1213, 1098, 1045, 860, 759, 690, 582, 499 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{12}H_{15}O_4$ $[M+H]^+$, 223.0970. Found 223.0972; HPLC, Daicel Chiralcel ADH, hexane/$^i$PrOH=4/1, flow rate=0.5 mL/min: $t_R$=19.9 min (*S*), $t_R$=22.2 min (*R*).

**5.2.2. (2*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-4-oxo-butyric acid ethyl ester (7b).** $^1$H NMR ($CDCl_3$) $\delta$=1.28 (t, 3H, $J$=7.1 Hz), 3.41 (dd, 1H, $J$=5.9, 17.4 Hz), 3.48 (dd, 1H, $J$=4.0, 17.4 Hz), 3.48 (brd, 1H, $J$=6.8 Hz), 3.87 (s, 3H), 4.26 (q, 2H, $J$=7.1 Hz), 4.60–4.70 (m, 1H), 6.91–6.97 (m, 2H), 7.90–7.97 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$=14.0, 41.7, 55.4, 61.7, 67.3, 113.8, 129.5, 130.4, 163.8, 173.8, 196.1. IR (neat) 3483, 2979, 2841, 1739, 1677, 1600, 1575, 1512, 1465, 1421, 1368, 1265, 1172, 1099, 1027, 988, 895, 834, 737, 579 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{13}H_{17}O_5$ $[M+H]^+$, 253.1076. Found 253.1097; HPLC, Daicel Chiralcel ADH, hexane/$^i$PrOH=4/1, flow rate=0.4 mL/min: $t_R$=43.1 min (*S*), $t_R$=45.7 min (*R*).

**5.2.3. (2*S*)-4-(4-Chloro-phenyl)-2-hydroxy-4-oxo-butyric acid ethyl ester (7c).** $^1$H NMR ($CDCl_3$) $\delta$=1.28 (t, 3H, $J$=7.1 Hz), 3.42 (dd, 1H, $J$=6.1, 17.3 Hz), 3.49 (dd, 1H, $J$=3.9, 17.3 Hz), 3.41–3.47 (brd, 1H), 4.26 (q, 2H, $J$=7.1 Hz), 4.62–4.70 (m, 1H), 7.42–7.48 (m, 2H), 7.86–7.93 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$=14.1, 42.2, 62.0, 67.1, 129.0, 129.6, 134.8, 140.1, 173.7, 196.3. IR (neat) 3480, 2982, 1739, 1684, 1590, 1573, 1402, 1213, 1093, 1045, 820, 531 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{12}H_{14}ClO_4$ $[M+H]^+$, 257.0580. Found 257.0584; HPLC, Daicel Chiralcel ADH, hexane/$^i$PrOH=4/1, flow rate=0.5 mL/min: $t_R$=24.2 min (*S*), $t_R$=26.5 min (*R*).

**5.2.4. (2*S*)-2-Hydroxy-4-oxo-4-*p*-tolyl-butyric acid ethyl ester (7d).** $^1$H NMR ($CDCl_3$) $\delta$=1.28 (t, 3H, $J$=7.1 Hz), 2.41 (s, 3H), 3.44 (dd, 1H, $J$=5.9, 17.4 Hz), 3.51 (dd, 1H, $J$=4.0, 17.4 Hz), 3.45–3.55 (brs, 1H), 4.26 (q, 2H, $J$=7.1 Hz), 4.66 (dt, 1H, $J$=4.2, 5.5 Hz), 7.26 (apparent d, 2H, $J$=8.0 Hz), 7.85 (apparent d, 2H, $J$=8.2 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$=14.0, 21.6, 42.0, 61.7, 67.2, 128.2, 129.3, 133.9, 144.4, 173.7, 197.1. IR (neat) 3483, 2981, 1742, 1682, 1606, 1405, 1365, 1212, 1098, 1044, 813, 578 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1120; HPLC, Daicel Chiralcel ADH, hexane/$^i$PrOH=4/1, flow rate=0.3 mL/min: $t_R$=36.1 min (*S*), $t_R$=38.2 min (*R*).

**5.2.5. (2*S*)-2-Hydroxy-4-naphthalen-2-yl-4-oxo-butyric acid ethyl ester (7e).** $^1$H NMR ($CDCl_3$) $\delta$=1.28 (t, 3H, $J$=7.1 Hz), 3.52 (d, 1H, $J$=5.9 Hz), 3.59 (dd, 1H, $J$=6.1, 17.3 Hz), 3.66 (dd, 1H, $J$=3.9, 17.3 Hz), 4.28 (q, 2H, $J$=7.1 Hz), 4.73 (dt, 1H, $J$=4.2, 5.4 Hz), 7.50–7.65 (m, 2H), 7.82–8.20 (m, 4H), 8.45 (s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$=14.1, 42.3, 61.9, 67.3, 123.6, 126.9, 127.8, 128.6, 128.8, 129.6, 130.2, 132.4, 133.8, 135.8, 173.9, 197.5. IR (neat) 3481, 3058, 2982, 1741, 1681, 1627, 1469, 1369, 1209, 1097, 1045, 859, 824, 749, 477 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{16}H_{17}O_4$ $[M+H]^+$, 273.1127. Found 273.1125; HPLC, Daicel Chiralcel ADH, hexane/$^i$PrOH=4/1, flow rate=0.5 mL/min: $t_R$=27.0 min (*S*), $t_R$=30.4 min (*R*).

**5.2.6. (2*S*)-2-Hydroxy-3-methyl-4-oxo-4-phenyl-butyric acid ethyl ester (7f, *syn/anti* mixture).** $^1$H NMR *syn* ($CDCl_3$) $\delta$=1.26 (t, 3H, $J$=7.0 Hz), 1.29 (d, 3H, $J$=7.0 Hz), 3.28 (br, 1H), 3.93 (dq, 1H, $J$=4.2, 7.0 Hz), 4.25 (q, 2H, $J$=7.0 Hz), 4.58 (d, 1H, $J$=4.2 Hz), 7.40–7.65 (m, 3H), 7.90–8.05 (m, 2H); *anti* ($CDCl_3$) $\delta$=1.20 (t, 3H, $J$=7.1 Hz), 1.36 (d, 3H, $J$=7.3 Hz), 3.61 (d, 1H, $J$=8.3 Hz), 3.98 (dq, 1H, $J$=4.6, 7.1 Hz), 4.10–4.25 (m, 2H), 4.39 (dd, 1H, $J$=4.6, 8.3 Hz), 7.40–7.65 (m, 3H); $^{13}$C NMR *syn* ($CDCl_3$) $\delta$=12.1, 14.0, 44.3, 61.9, 71.6, 128.4, 128.7, 133.3, 135.7, 173.1, 201.6; *anti* ($CDCl_3$) $\delta$=14.0, 14.1, 44.0, 61.5, 73.1, 128.3, 128.7, 133.4, 135.9, 173.1; IR (neat) *syn* 3480, 3063, 2978, 2936, 1734, 1678, 1596, 1579, 1449, 1369, 1217, 1133, 1062, 1023, 1001, 975, 952, 862, 794, 708; *anti* 3481, 3059, 2981, 2941, 1738, 1685, 1588, 1454, 1372, 1255, 1209, 1144, 1092, 1024, 973, 701 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1118; HPLC, Daicel Chiralcel AS+ADH+AD, hexane/$^i$PrOH=4/1, flow rate=0.5 mL/min: $t_R$=46.7 min (2*S*,3*S*), $t_R$=50.6 min (2*R*,3*R*), $t_R$=54.3 min (2*S*,3*R*), $t_R$=61.9 min (2*R*,3*S*).

**5.2.7. (2*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-3-methyl-4-oxo-butyric acid ethyl ester (7g, *syn/anti* mixture).** $^1$H NMR *syn* ($CDCl_3$) $\delta$=1.28 (t, 3H, $J$=7.1 Hz), 1.29 (d, 3H, $J$=7.1 Hz), 3.35 (br, 1H), 3.84–3.96 (m, 4H), 4.27 (q, 2H, $J$=7.1 Hz), 4.58 (t, 1H, $J$=4.2 Hz), 6.96 (apparent d, 2H, $J$=9.0 Hz), 7.30–7.45 (m, 5H), 7.95 (apparent d, 2H, $J$=8.8 Hz); *anti* ($CDCl_3$) $\delta$=1.19 (t, 3H, $J$=7.1 Hz), 1.36 (d, 3H, $J$=7.3 Hz), 3.75 (d, 1H, $J$=9.3 Hz), 3.88 (s, 3H), 3.94 (dq, 1H, $J$=4.6, 7.3 Hz), 4.15 (apparent dq, 2H, $J$=3.2, 7.1 Hz), 4.36 (dd, 1H, $J$=4.6, 9.3 Hz), 6.92–6.99 (m, 2H), 7.90–7.97 (m, 2H); $^{13}$C NMR *syn* ($CDCl_3$) $\delta$=12.3, 14.0, 43.7, 55.4, 61.8, 71.7, 113.9, 128.5, 130.7, 163.7, 173.1, 200.4; *anti* ($CDCl_3$) $\delta$=14.0, 14.6, 43.2, 55.5, 61.4, 73.4, 113.9, 128.7, 130.8, 163.8, 173.2, 201.9; IR (neat) *syn* 3477, 2979, 2935, 2850, 1730, 1670, 1600, 1573, 1510, 1463, 1420, 1308, 1261, 1173, 1125, 1027, 976, 843, 770, 604; *anti* 3478, 2979, 2941, 2843, 1738, 1671, 1599, 1580, 1510, 1457, 1419, 1370, 1308, 1257, 1216, 1172, 1092, 1026, 974, 841 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{14}H_{19}O_5$ $[M+H]^+$, 267.1232. Found 267.1232; HPLC, Daicel

Chiralcel ADH, hexane/$^{i}$PrOH=4/1, flow rate=0.2 mL/min: $t_R$=60.5 min (2*R*,3*R*), $t_R$=65.4 min (2*S*,2*S*), $t_R$=75.2 min (2*R*,3*S*), $t_R$=78.9 min (2*S*,3*R*).

**5.2.8. (2*S*)-4-(4-Chloro-phenyl)-2-hydroxy-3-methyl-4-oxo-butyric acid ethyl ester (7i, *syn/anti* mixture).** $^1$H NMR *syn* ($CDCl_3$) $\delta$=1.26 (t, 3H, *J*=7.0 Hz), 1.28 (d, 3H, *J*=7.0 Hz), 3.27 (brs, 1H), 3.87 (dq, 1H, *J*=4.4, 7.0 Hz), 4.25 (q, 2H, *J*=7.0 Hz), 4.55 (d, 1H, *J*=4.4 Hz), 7.40–7.55 (m, 2H), 7.84–7.97 (m, 2H); *anti* ($CDCl_3$) $\delta$=1.21 (t, 3H, *J*=7.1 Hz), 1.34 (d, 3H, *J*=7.1 Hz), 3.53 (d, 1H, *J*=8.2 Hz), 3.91 (dq, 1H, *J*=5.0, 7.1 Hz), 4.08–4.24 (m, 2H), 4.38 (dd, 1H, *J*=5.0, 8.2 Hz), 7.42–7.52 (m, 2H), 7.80–7.95 (m, 2H); $^{13}$C NMR *syn* ($CDCl_3$) $\delta$=12.1, 14.0, 44.4, 62.0, 71.5, 129.0, 129.8, 134.1, 139.7, 173.1, 200.3; *anti* ($CDCl_3$) $\delta$=13.9, 14.0, 44.1, 61.6, 73.0, 129.0, 129.8, 134.3, 139.9, 173.0, 201.8; IR (neat) *syn* 3485, 2982, 2938, 1730, 1682, 1589, 1571, 1488, 1455, 1401, 1217, 1132, 1092, 1013, 977, 843, 758, 692, 533, 478; *anti* 3478, 3092, 2982, 2935, 1738, 1686, 1589, 1455, 1402, 1255, 1208, 1144, 1092, 1022, 976, 842, 751, 527 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{13}H_{16}ClO_4$ $[M+H]^+$, 271.0737. Found 271.0745; HPLC, Daicel Chiralcel AS, hexane/$^{i}$PrOH=4/1, flow rate=0.5 mL/min: $t_R$=15.1 min (2*S*,3*S*), $t_R$=16.6 min (2*S*,3*R*), $t_R$=21.4 min (2*R*,3*S*), $t_R$=23.9 min (2*R*,3*R*).

**5.2.9. (2*S*)-3-Benzoyl-2-hydroxy-pentanoic acid ethyl ester (7j, *syn/anti* mixture).** $^1$H NMR *syn* ($CDCl_3$) $\delta$=0.93 (t, 3H, *J*=7.5 Hz), 1.19 (t, 3H, *J*=7.1 Hz), 1.70–2.05 (m, 2H), 3.18 (brs, 1H), 3.83 (dt, 1H, *J*=5.3, 8.3 Hz), 4.19 (q, 2H, *J*=7.1 Hz), 4.51 (d, 1H, *J*=5.3 Hz), 7.42–7.54 (m, 2H), 7.54–7.62 (m, 1H), 7.90–8.02 (m, 2H); *anti* ($CDCl_3$) $\delta$=1.04 (t, 3H, *J*=7.6 Hz), 1.15 (t, 3H, *J*=7.1 Hz), 1.80–1.95 (m, 2H), 3.70 (d, 1H, *J*=9.5 Hz), 3.83 (dt, 1H, *J*=4.2, 7.1 Hz), 4.09 (q, 2H, *J*=7.1 Hz), 4.43 (dd, 1H, *J*=4.2, 9.5 Hz), 7.46–7.52 (m, 2H), 7.56–7.63 (m, 1H), 7.88–7.95 (m, 2H); $^{13}$C NMR *syn* ($CDCl_3$) $\delta$=12.0, 13.9, 21.3, 51.2, 61.9, 71.1, 128.3, 128.6, 133.2, 137.0, 173.6, 201.5; *anti* ($CDCl_3$) $\delta$=12.0, 13.9, 22.3, 50.1, 61.4, 71.3, 128.3, 128.7, 133.5, 136.6, 173.4, 203.9; IR (neat) *syn* 3477, 2972, 2876, 1738, 1675, 1596, 1447, 1372, 1255, 1220, 1118, 1023, 931, 849, 779, 701; *anti* 3485, 3062, 2966, 2941, 2875, 1738, 1682, 1596, 1579, 1448, 1368, 1268, 1208, 1134, 1100, 1028, 914, 849, 785, 699 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{14}H_{19}O_4$ $[M+H]^+$, 251.1283. Found 251.1277; HPLC, Daicel Chiralcel AS, hexane/$^{i}$PrOH=4/1, flow rate=0.5 mL/min: $t_R$=13.7 min (2*S*,3*S*), $t_R$=15.3 min (2*S*,3*R*), $t_R$=17.6 min (2*R*,3*R*), $t_R$=23.1 min (2*R*,3*S*).

**5.2.10. (2*S*)-2-Hydroxy-3-methyl-4-oxo-hexanoic acid ethyl ester (7k, *syn/anti* mixture).** $^1$H NMR *syn* ($C_6D_6$) $\delta$=0.89 (t, 3H, *J*=7.1 Hz), 0.99 (d, 3H, *J*=7.2 Hz), 1.97–2.08 (m, 2H), 2.70 (dq, 1H, *J*=4.9, 7.2 Hz), 3.39 (d, 1H, *J*=6.7 Hz), 3.80–4.00 (m, 2H), 4.11 (dd, 1H, *J*=4.9, 6.7 Hz); *anti* ($C_6D_6$) $\delta$=0.87 (t, 3H, *J*=7.1 Hz), 0.93 (t, 3H, *J*=7.3 Hz), 1.02 (d, 3H, *J*=7.2 Hz), 1.95–2.22 (m, 2H), 2.65 (dq, 1H, *J*=4.4, 7.2 Hz), 3.05–3.23 (m, 1H), 3.80–4.00 (m, 2H), 4.38–4.47 (m, 1H); $^{13}$C NMR *syn* ($CDCl_3$) $\delta$=7.58, 12.8, 14.0, 34.6, 49.4, 61.3, 73.0, 173.5, 211.3; *anti* ($C_6D_6$) $\delta$=7.7, 11.0, 14.0, 34.0, 49.5, 61.6, 71.7, 173.7, 209.9; IR (neat) *syn* 3484, 2981, 2940, 1739, 1716, 1459, 1409, 1375, 1268, 1209, 1108, 1066, 1025, 975, 862, 808, 748; *anti* 3488, 2981, 2940, 1733, 1716, 1459, 1373, 1218, 1145, 1025, 977, 862, 800, 752 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_9H_{17}O_4$ $[M+H]^+$, 189.1127. Found 189.1120.

**5.2.11. (1*S*)-Hydroxy-(2-oxo-cyclohexyl)-acetic acid ethyl ester (7l, *syn/anti* mixture).** $^1$H NMR *anti* ((1*S*,1′*R*), tentatively assignment) ($C_6D_6$) $\delta$=0.95 (t, 3H, *J*=7.1 Hz), 0.94–1.20 (m, 2H), 1.30–1.42 (m, 2H), 1.56–1.84 (m, 3H), 2.02–2.12 (m, 1H), 2.60–2.70 (m, 1H), 3.35 (d, 1H, *J*=7.2 Hz), 3.84 (dd, 1H, *J*=3.2, 7.2 Hz), 4.02 (dq, 2H, *J*=1.9, 7.1 Hz); distingishable *syn* peaks $\delta$=0.88 (t, 3H, *J*=7.1 Hz), 2.12–2.21 (m, 1H), 2.48–2.57 (m,1H), 2.94 (d, 1H, *J*=5.0 Hz), 4.60 (dd, 1H, *J*=3.2, 5.0 Hz); $^{13}$C NMR *anti* ($CDCl_3$) $\delta$=14.1, 24.8, 26.9, 30.1, 42.0, 53.7, 61.6, 71.1, 173.4, 211.2; distinguishable *syn* peaks $\delta$=14.2, 24.6, 27.1, 41.9, 53.8, 61.7, 69.2, 173.6, 210.4; HRMS (FAB). Exact mass calcd for $C_{10}H_{17}O_4$ $[M+H]^+$, 201.1127. Found 201.1127.

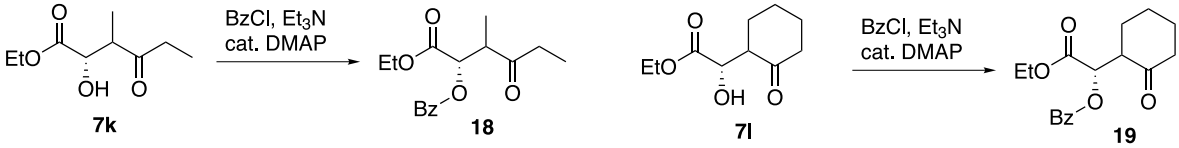
## 6. Determination of the ee's of 7k and 7l

In order to determine the ee's of **7k** and **7l** whose ee's could not be determined by HPLC analysis as their UV absorbance were very weak, they were converted to **18** and **19**, respectively (Scheme 8).

### 6.1. Synthesis of 18

To a solution of **7k** (17.9 mg, 0.095 mmol) in $CH_2Cl_2$ (0.4 mL) was added a solution of $Et_3N$ (19.9 μL, 0.143 mmol) in $CH_2Cl_2$ (0.3 mL) followed by a solution of BzCl (16.6 μL, 0.143 mmol) in $CH_2Cl_2$ (0.3 mL) and DMAP (catalytic amount) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C, and water was added, followed by addition of a 1N HCl aqueous solution. The reaction mixture was extracted with $Et_2O$, and the organic phase was washed with a saturated $NaHCO_3$ aqueous solution and brine, and dried over anhydrous $MgSO_4$. After evaporation of solvents, the crude adduct was purified by chromatography on silica gel to afford **18** (22.2 mg, 80% yield). **19** was also synthesized by using the same method mentioned above (74% yield).

**6.1.1. (1*S*)-Benzoic acid 1-ethoxycarbonyl-2-methyl-3-oxo-pentyl ester (18, *syn/anti* mixture).** $^1$H NMR *syn* ($CDCl_3$) $\delta$=1.09 (t, 3H, *J*=7.1 Hz), 1.23 (t, 3H, *J*=7.1 Hz),




**Scheme 8.**

1.25 (t, 3H, $J$=7.1 Hz), 2.59 (q, 2H, $J$=7.1 Hz), 3.23 (quint, 1H, $J$=7.1 Hz), 4.22 (q, 1H, $J$=7.1 Hz), 4.22 (q, 1H, $J$=7.1 Hz), 5.39 (d, 1H, $J$=7.1 Hz), 7.35–7.50 (m, 2H), 7.50–7.60 (m, 1H), 7.92–8.04 (m, 2H); *anti* $\delta$=1.05 (t, 3H, $J$=7.3 Hz), 1.24 (t, 3H, $J$=7.1 Hz), 1.26 (t, 3H, $J$=7.1 Hz), 2.57 (q, 2H, $J$=7.3 Hz), 3.21 (dq, 1H, $J$=5.1, 7.1 Hz), 4.21 (q, 2H, $J$=7.1 Hz), 5.69 (d, 1H, $J$=5.1 Hz), 7.42 (apparent t, 2H, $J$=7.5 Hz), 7.50–7.60 (m, 1H), 7.95–8.05 (m, 2H); $^{13}$C NMR *anti* ($CDCl_3$) $\delta$=7.7, 11.6, 14.1, 34.1, 47.1, 61.8, 72.6, 128.4, 129.2, 129.8, 133.4, 165.6, 168.9, 209.6; distinguishable *syn* peaks $\delta$=12.6, 35.0, 61.6, 73.9, 129.1, 129.9, 130.2, 133.7, 209.7; IR (neat) 2981, 2940, 1725, 1602, 1454, 1375, 1348, 1280, 1211, 1103, 1070, 1027, 977, 713 $cm^{-1}$; HRMS (FAB). Exact mass calcd for $C_{16}H_{21}O_5$ $[M+H]^+$, 293.1389. Found 293.1380; HPLC, Daicel Chiralcel ADH+ADH, hexane/$^i$PrOH=19/1, flow rate=0.5 mL/min: $t_R$=42.7 min (1*R*,2*R*), $t_R$=51.3 min (1*S*,2*S*), $t_R$=54.7 min (1*S*,2*R*), $t_R$=56.8 min (1*R*,2*S*).

**6.1.2. (1*S*)-Benzoic acid ethoxycarbonyl-(2-oxo-cyclohexyl)-methyl ester (19, *syn/anti* mixture).** $^1$H NMR *anti* ((1*S*,1′*R*) tentatively assignment) ($CDCl_3$) $\delta$=1.26 (t, 3H, $J$=7.1 Hz), 1.60–1.85 (m, 3H), 1.85–2.20 (m, 3H), 2.25–2.60 (m, 2H), 3.14–3.30 (m, 1H), 4.23 (q, 2H, $J$=7.1 Hz), 5.51 (d, 1H, $J$=4.8 Hz), 7.40–7.50 (m, 2H), 7.52–7.61 (m, 1H), 7.98–8.14 (m, 2H); distinguishable *syn* peaks $\delta$=1.27 (t, 3H, $J$=7.0 Hz), 2.96–3.10 (m, 1H), 4.23 (q, 2H, $J$=7.0 Hz), 5.86 (d, 1H, $J$=3.3 Hz); $^{13}$C NMR *anti* ($CDCl_3$) $\delta$=14.0, 24.6, 26.8, 29.5, 41.8, 51.7, 61.5, 70.9, 128.4, 129.4, 129.9, 133.3, 165.9, 169.2, 207.5; *syn* $\delta$=14.1, 26.7, 27.8, 41.7, 51.6, 61.6, 70.1, 128.3, 129.6, 129.8, 133.2, 165.5, 169.6, 207.3; HRMS (FAB). Exact mass calcd for $C_{17}H_{21}O_5$ $[M+H]^+$, 305.1389. Found 305.1382; HPLC, Daicel Chiralcel ADH+AS, hexane/$^i$PrOH=9/1, flow rate=0.9 mL/min: $t_R$=25.2 min (1*S*,1′*R*), $t_R$=27.4 min (*syn*, the absolute configuration was not determined.), $t_R$=29.9 min (1*R*,1′*S*), $t_R$=36.6 min (*syn*).

## 7. Reduction of 6a

### 7.1. Procedure for the synthesis of 10

Ligand **3t** (9.9 mg, 0.022 mmol) in $CH_2Cl_2$ (1.5 mL) was added to the $CuClO_4 \cdot 4CH_3CN$ (6.5 mg, 0.020 mmol) flask under argon The yellow solution was stirred for over 8 h, and cooled to 0 °C. Freshly distilled ethyl glyoxylate (100 μL, 0.40 mmol) in $CH_2Cl_2$ (0.8 mL) was added to the mixture, and then enecarbamate **2a** (50.7 mg, 0.20 mmol) in $CH_2Cl_2$ (0.8 mL) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. The reaction mixture was allowed to warm to rt, and was extracted with $CH_2Cl_2$. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated, and then the residue was dried with benzene azeotropy three times and then under vacuum. THF (2.0 mL) and MeOH (0.5 mL) were added to the residue, and then the solution was cooled to −78 °C. Diethyl methoxyborane (79 μL, 0.6 mmol) was added, and the mixture was stirred for 15 min. To the mixture was added $NaBH_4$ (22.7 mg, 0.6 mmol) in one portion. The mixture was stirred for 2 h at −78 °C. The reaction was quenched by addition of AcOH (0.3 mL) and was allowed to warm to rt. The mixture was alkalized at 0 °C by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with $Et_2O$ twice. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvents were evaporated, the crude product was purified by chromatography on silica gel to afford the desired compound **10** (46.5 mg, 65% yield in two steps, *syn/anti*=94/6).

**7.1.1. 4-Benzyloxycarbonylamino-2-hydroxy-4-phenyl-butyric acid ethyl ester: (10, *syn/anti*=94/6).** $^1$H NMR ($CDCl_3$) $\delta$=1.23 (t, 3H x 19/20, $J$=7.1 Hz), 1.25 (t, 3H x 1/20, $J$=7.0 Hz), 1.95–2.40 (m, 2H), 3.33 (brs, 1H x 19/20), 3.51 (brs, 1H x 1/20), 4.00–4.40 (m, 3H), 4.85–5.20 (m, 3H), 5.52 (d, 1H x 19/20, $J$=7.3 Hz), 5.96 (d, 1H x 1/20, $J$=8.2 Hz), 7.00–7.60 (m, 10H); $^{13}$C NMR ($CDCl_3$) *syn*: $\delta$=14.1, 40.3, 52.6, 61.8, 66.8, 68.4, 126.4, 127.6, 128.1, 128.4, 128.7, 136.3, 141.4, 155.7, 174.4; *anti*: (distinguishable peak) 40.2, 52.4, 67.8, 126.2, 127.4, 141.1, 156.0, 174.3; LRMS (FAB) $m/z$=358 $[M+H]^+$

### 7.2. Determination of relative configuration of compound 10

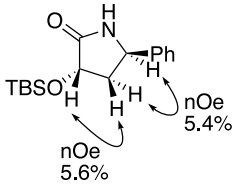
**7.2.1. Synthesis of 11.** To a solution of **10** (31.3 mg, 0.088 mmol) in $CH_2Cl_2$ (0.6 mL) was added 2,6-lutidine (12.0 mg, 0.114 mmol) in $CH_2Cl_2$ (0.2 mL) and TBDMSOTf (27.8 mg, 0.105 mmol) in $CH_2Cl_2$ (0.2 mL) successively at 0 °C. The reaction mixture was allowed to warm to rt, and was stirred for 10 h. $H_2O$ was added and the mixture was extracted with $CH_2Cl_2$. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the crude product was purified on silica gel column chromatography to give **11** (37.9 mg, 92% yield).

**7.2.2. 4-Benzyloxycarbonylamino-2-(*tert*-butyl-dimethyl-silanyloxy)-4-phenyl-butyric acid ethyl ester (11, diastereomer mixture).** $^1$H NMR ($CDCl_3$) $\delta$=*syn*: −0.03 (s, 3H), 0.02 (s, 3H), 0.90 (s, 9H), 1.15–1.27 (m, 3H), 2.00–2.35 (m, 2H), 3.90–4.30 (m, 3H), 4.80–5.15 (m, 3H), 5.50 (brs, 1H), 7.15–7.40 (m, 10 H); *anti*: (distinguishable peak) $\delta$=−0.02 (s, 3H), 0.03 (s, 3H), 5.62 (brd, 1H, $J$=7.7 Hz); $^{13}$C NMR ($CDCl_3$) *syn*: $\delta$=−5.4, −5.0, 14.0, 18.1, 25.7, 41.0, 52.9, 61.0, 66.6, 70.3, 126.4, 127.4, 128.0, 128.1, 128.4, 128.6, 136.4, 141.8, 155.3, 173.2; *anti*: (distinguishable peak) −5.0, 14.1, 41.8, 52.3, 69.8, 126.0, 127.3, 128.6, 142.2, 155.6, 173.1; IR (neat) 3343, 2940, 1720, 1518, 1254, 1131, 1038, 839, 781, 699 $cm^{-1}$; HRMS (FAB). Exact mass calcd for $C_{26}H_{38}NO_5Si$ $[M+H]^+$, 472.2519. Found 472.2508.

**7.2.3. Synthesis of 12.** To a solution of **11** (21.4 mg, 0.0454 mmol) in AcOEt (2.0 mL) was added AcOH (16.8 mg, 0.0.272 mmol) and 5% wet Pd/C (9.7 mg, 10 mol%) at rt. After replacement of argon by hydrogen, the mixture was stirred at rt until the starting material completely disappeared (11 h). Pd/C was filtered off and saturated aqueous $NaHCO_3$ was added to the filtrate. The mixture was extracted with AcOEt, and then the organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the solvent was evaporated, the crude product was purified on silica gel column chromatography to give **12**

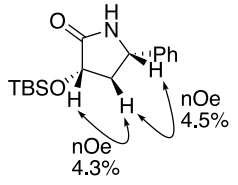
(13.4 mg, quantitative yield). Diastereomers **12** were separated by silica gel column chromatography.

**7.2.4. (3*S*,5*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenyl-pyrrolidin-2-one (12-major).** $^1$H NMR ($CDCl_3$) $\delta$= 0.14 (s, 3H), 0.16 (s, 3H), 0.91 (s, 9H), 2.21 (ddd, 1H, $J$=5.1, 7.1, 13.2 Hz), 2.46 (ddd, 1H, $J$=5.1, 7.5, 13.2 Hz), 4.38 (dd, 1H, $J$=5.1, 7.1 Hz), 4.83 (dd, 1H, $J$=5.0, 7.5 Hz), 6.02 (brs, 1H), 7.20–7.43 (m, 5H); $^{13}$C NMR ($CDCl_3$) $\delta$=−5.1, −4.5, 18.3, 25.8, 41.5, 55.1, 69.9, 125.5, 127.9, 129.0, 142.1, 176.3; IR (neat) 3226, 2927, 2892, 2855, 1715, 1496, 1471, 1331, 1253, 1151, 1091, 1028, 963, 880, 839, 780, 699 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{16}H_{26}NO_2Si$ $[M+H]^+$, 292.1733. Found 292.1733 (Scheme 9).




**Scheme 9.**

**7.2.5. (3*S*,5*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenyl-pyrrolidin-2-one (12-minor).** $^1$H NMR ($CDCl_3$) $\delta$= 0.15 (s, 3H), 0.20 (s, 3H), 0.91 (s, 9H), 1.94 (dt, 1H, $J$=9.2, 12.6 Hz), 2.75–2.87 (m, 1H), 4.42 (dd, 1H, $J$=7.9, 9.2 Hz), 4.53 (dd, 1H, $J$=6.2, 8.6 Hz), 5.76 (brs, 1H), 7.30–7.40 (m, 5H); $^{13}$C NMR ($CDCl_3$) $\delta$=−5.1, −4.5, 18.3, 25.8, 42.0, 53.9, 70.8, 126.1, 128.1, 128.9, 176.0; IR (neat) 3220, 2936, 2858, 2359, 1717, 1463, 1330, 1247, 1151, 882, 838, 781, 698 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{16}H_{26}NO_2Si$ $[M+H]^+$, 292.1733. Found 292.1736 (Scheme 10).




**Scheme 10.**

## 8. Determination of the absolute and relative configuration of 7f

### 8.1. Determination of the relative configuration of 7f

To a solution of *anti*-**7f** (45.6 mg, 0.193 mmol) in MeOH (1.0 mL) was added $NaBH_4$ (14.6 mg, 0.39 mmol) at 0 °C. The reaction mixture was stirred for 10 min, and the reaction was quenched by addition of acetone. The mixture was kept stirred for 5 min, and then saturated $NH_4Cl$ aqueous solution was added. The mixture was extracted with $CH_2Cl_2$ three times, and the extract was dried over anhydrous $MgSO_4$. The solvents were evaporated to give a crude keto alcohol. To a solution of the crude product in $CH_2Cl_2$ (1 mL) was added $TsOH\cdot H_2O$, and the reaction mixture was stirred for 13.5 h at rt. The reaction was quenched by addition of a saturated $NaHCO_3$ aqueous solution, and was extracted with $CH_2Cl_2$ three times. The extract was dried over anhydrous $MgSO_4$. The solvents were evaporated to give a residue, followed by purification on silica gel chromatography to afford **14** as a diastereomer mixture (19.8 mg, 53% yield, **14**/*epi*-**14**=55/45). **14** was recrystallized from $CH_2Cl_2$/hexane to give single crystals which were suitable for X-ray structure analysis. From *syn*-**7f**, **20** was obtained as a diastereomer mixture (84% yield, **20**/*epi*-**20**=86/14) according to the same procedure as mentioned above. The relative stereochemisty of **20** was determined by NOE analysis. Lactones **14** and **20** were used for determination of the absolute configuration as follows.

**8.1.1. (3*S*,4*R*,5*S*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (14).** Mp 150–151 °C; $^1$H NMR ($CDCl_3$) $\delta$=0.65 (d, 3H, $J$=7.3 Hz), 2.75 (brs, 1H), 2.98–3.08 (m, 1H), 4.79 (d, 1H, $J$=6.8 Hz), 5.57 (d, 1H, $J$= 4.6 Hz), 7.25–7.30 (m, 2H), 7.30–7.38 (m, 1H), 7.38–7.45 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$=7.4, 41.1, 72.1, 80.2, 125.2, 128.2, 128.6, 135.1, 177.0; IR (neat) 3443, 2963, 1758, 1452, 1414, 1294, 1194, 1148, 1051, 956, 754, 701, 622, 478 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0872.

**8.1.2. (3*S*,4*R*,5*R*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (*epi*-14).** $^1$H NMR ($CDCl_3$) $\delta$=1.22 (d, 3H, $J$=7.1 Hz), 2.62 (tq, 1H, $J$=5.1, 6.8 Hz), 2.86 (brs, 1H), 4.47 (d, 1H, $J$=6.8 Hz), 5.26 (d, 1H, $J$=5.1 Hz), 7.20–7.45 (m, 5H); $^{13}$C NMR ($CDCl_3$) $\delta$=10.8, 43.2, 69.7, 85.8, 125.3, 128.6, 128.8, 137.7, 176.9; IR (neat) 3430, 3039, 2924, 2857, 1772, 1455, 1275, 1202, 1143, 1093, 986, 889, 805, 742, 702 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0864.

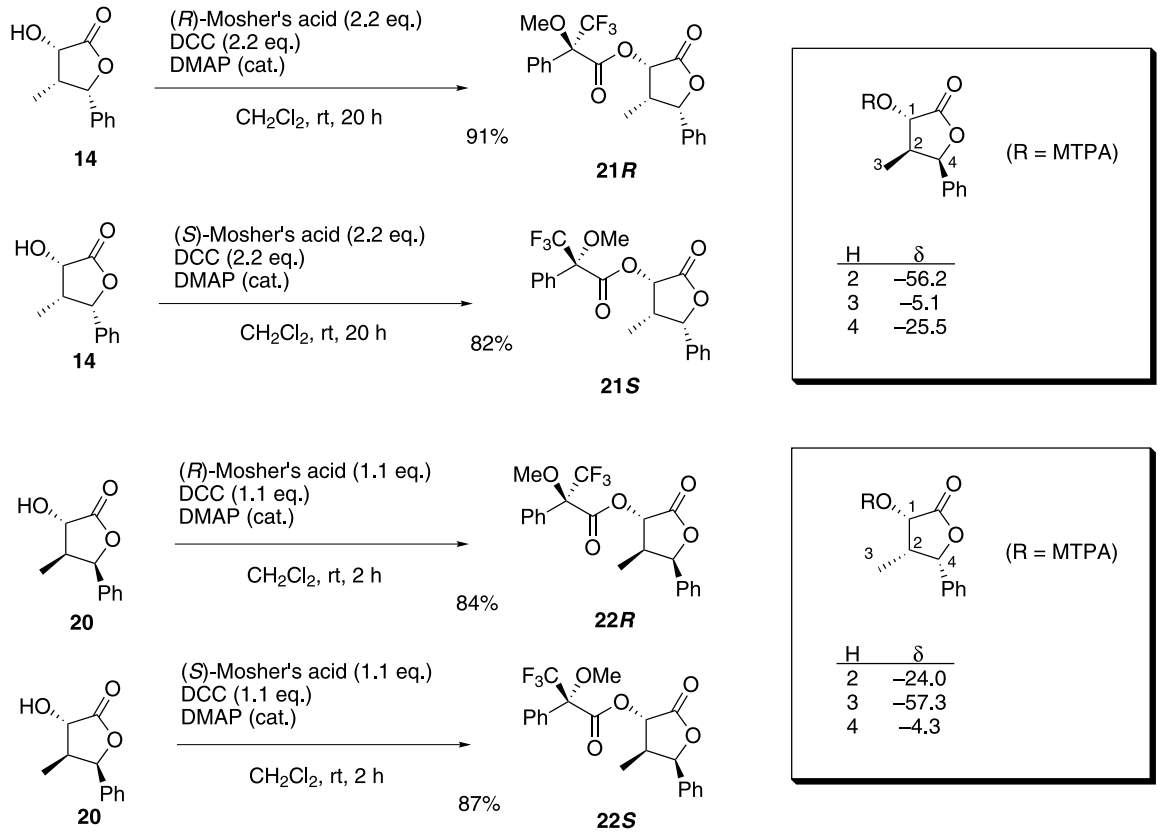
**8.1.3. (3*S*,4*S*,5*R*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (20).** $^1$H NMR ($CDCl_3$) $\delta$=0.87 (d, 3H, $J$=7.0 Hz), 2.70–2.92 (m, 1H), 3.18 (brs, 1H), 4.24 (d, 1H, $J$=9.9 Hz), 5.63 (d, 1H, $J$=8.1 Hz), 7.05–7.18 (m, 2H), 7.30–7.45 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$=13.3, 42.1, 72.2, 82.4, 125.7, 128.5, 128.6, 135.5, 177.5; IR (neat) 3362, 2970, 1776, 1455, 1334, 1184, 1145, 1096, 991, 897, 755, 701, 464 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0872.

**8.1.4. (3*S*,4*S*,5*S*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (*epi*-20).** $^1$H NMR ($CDCl_3$) $\delta$=1.24 (d, 3H, $J$=6.4 Hz), 2.41 (tq, 1H, $J$=6.4, 10.6 Hz), 3.24 (brs, 1H), 4.25 (d, 1H, $J$=11.0 Hz), 4.87 (d, 1H, $J$=10.1 Hz), 7.30–7.50 (m, 5H); $^{13}$C NMR ($CDCl_3$) $\delta$=13.3, 47.5, 74.7, 84.1, 126.5, 128.8, 129.2, 136.2, 176.8; IR (neat) 3319, 2967, 2921, 1776, 1459, 1318, 1237, 1152, 1110, 981, 765, 700, 540 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0857.

### 8.2. Determination of the absolute configuration of 7f

Lactones **14** and **20** were converted into **21** and **22** respectively, by using a standard method as shown below (Scheme 11).

$\Delta\delta$ ($\delta_S-\delta_R$) in the $^1$H NMR analysis showed minus values for all H2, H3, and H4. As expected from an analogy of **7a**, the absolute configuration of C3 was determined to be *S*.[15]




**Scheme 11.**

From the knowledge of the absolute stereochemistry of **14** and **20**, the absolute configurations of both *anti*-**7f** and *syn*-**7f** were determined.

**8.2.1. (3*S*,4*S*,5*S*,2′*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (21*R*).** $^1$H NMR ($CDCl_3$) $\delta$=0.66 (d, 3H, $J$=7.1 Hz), 3.10–3.26 (m, 1H), 3.54 (d, 3H, $J$=0.9 Hz), 5.67 (d, 1H, $J$=4.8 Hz), 6.04 (d, 1H, $J$=7.1 Hz), 7.20–7.30 (m, 2H), 7.30–7.50 (m, 6H), 7.55–7.68 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$=8.4, 39.3, 55.5, 73.3, 80.1, 125.2, 127.8, 128.5, 128.5, 128.7, 129.9, 131.0, 134.4, 165.7, 170.4; IR (neat) 3063, 3033, 2987, 2947, 2850, 1802, 1754, 1504, 1455, 1364, 1245, 1179, 1111, 1089, 1057, 975, 698 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1277.

**8.2.2. (3*S*,4*S*,5*S*,2′*S*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (21*S*).** $^1$H NMR ($CDCl_3$) $\delta$=0.47 (d, 3H, $J$=7.1 Hz), 3.00–3.20 (m, 1H), 3.66 (d, 3H, $J$=0.9 Hz), 5.66 (d, 1H, $J$=5.0 Hz), 6.07 (d, 1H, $J$=7.1 Hz), 7.20–7.30 (m, 2H), 7.30–7.50 (m, 6H), 7.60–7.70 (m, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$=8.1, 39.4, 55.8, 73.0, 80.2, 125.2, 127.3, 128.5, 128.5, 128.7, 129.9, 131.6, 134.4, 165.7, 170.8; IR (neat) 3065, 2941, 2857, 1802, 1755, 1497, 1455, 1393, 1367, 1243, 1178, 1125, 1058, 977, 705 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1277.

**8.2.3. (3*S*,4*R*,5*R*,2′*R*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (22*R*).** $^1$H NMR ($C_6D_6$) $\delta$=0.30 (d, 3H, $J$=7.0 Hz), 2.38–2.50 (m, 1H), 3.46 (d, 3H, $J$=0.9 Hz), 4.91 (d, 1H, $J$=8.6 Hz), 5.37 (d, 1H, $J$=11 Hz), 6.65–6.73 (m, 2H), 6.96–7.05 (m, 3H), 7.08–7.12 (m, 1H), 7.18–7.24 (m, 2H), 7.91 (apparent d, 2H, $J$=7.9 Hz); $^{13}$C NMR ($C_6D_6$) $\delta$=12.7, 39.0, 55.4, 74.2, 81.6, 125.9, 128.6, 128.7, 128.8, 130.0, 132.1, 135.3, 166.0, 170.6; IR (neat) 3033, 2974, 2945, 2850, 1800, 1757, 1497, 1453, 1340, 1243, 1170, 1116, 1056, 998, 909, 757, 699 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1245.

**8.2.4. (3*S*,4*R*,5*R*,2′*S*)-3,3,3-Trifluoro-2-methoxy-2-phenyl-propionic acid 4-methyl-2-oxo-5-phenyl-tetrahydro-furan-3-yl ester (22*S*).** $^1$H NMR ($C_6D_6$) $\delta$=0.28 (d, 3H, $J$=6.9 Hz), 2.15–2.35 (m, 1H), 3.65 (d, 3H, $J$=0.7 Hz), 4.83 (d, 1H, $J$=8.2 Hz), 5.61 (d, 1H, $J$=10.6 Hz), 6.64–6.72 (m, 2H), 6.90–7.05 (m, 3H), 7.05–7.25 (m, 3H), 7.80–7.90 (m, 2H); $^{13}$C NMR ($C_6D_6$) $\delta$=12.5, 39.4, 55.7, 73.6, 81.8, 122.2, 125.9, 127.9, 128.6, 128.8, 128.8, 130.0, 132.6, 135.2, 166.3, 171.2; IR (neat) 3065, 3033, 2945, 2851, 1800, 1759, 1496, 1454, 1342, 1273, 1247, 1172, 1123, 1081, 1057, 994, 903, 795, 763, 723 cm$^{-1}$; HRMS (FAB). Exact mass calcd for $C_{21}H_{20}F_3O_5$ $[M+H]^+$, 409.1263. Found 409.1282.

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